Oral Sedation During Cervical Dilator Placement: A Randomized Controlled Trial

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JHM IRB - eForm A – Protocol

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1. Abstract
   a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Abortion during the second trimester of pregnancy accounts for approximately 11% of abortions performed in the United States[1] and dilation and evacuation (D&E) is the most common method used.[2] Cervical preparation with osmotic dilators is common practice for D&E beyond 14 weeks.[2] Generally, osmotic dilators are the most effective form of cervical preparation.

Despite the widespread use of osmotic dilators for cervical preparation for D&E, there are minimal data regarding patient pain during dilator placement. Those studies that evaluate pain with dilator insertion and during the interval between insertion and the D&E procedure do so as a secondary outcome and find that pain with dilator placement is generally moderate.[3-5] Thus, it is important that we investigate options for pain control during cervical dilator placement.

Few studies have examined pain management specifically during cervical dilator placement. Additionally, no prior studies have examined the effect of oral sedation on pain during cervical dilator placement. Oral sedation has advantages over IV sedation as it is associated with decreased cost, generally fewer side effects, and is more feasible in an outpatient setting.

Anecdotally, it is not uncommon for women to request sedation for dilator placement, but there are currently no data to support effectiveness of oral sedation for dilator placement. By making patients more comfortable, pain improvement during dilator placement may increase the number of dilators placed and the subsequent dilation at time of D&E. Our hypothesis is that oral sedation will have a clinically significant impact on decreasing pain scores during and immediately after cervical dilator placement.

2. Objectives (include all primary and secondary objectives)

   1. <u>Primary objective:</u>

a. Determine if oral sedation has a clinically significant impact on pain scores (20 mm difference on a 100 mm VAS[6]) during and immediately after cervical dilator placement as compared to placebo among women presenting for second trimester surgical abortion Hypothesis: Oral sedation will significantly improve pain compared to placebo during cervical dilator placement.

2. Secondary objectives:
   a. To describe the symptoms and adverse events with oral sedation for cervical dilator placement

      Hypothesis: There will be differences in symptoms and adverse events with oral sedation as compared to placebo. These differences are unlikely to be significant and this study is not powered to detect these differences.
   b. To evaluate whether oral sedation for cervical dilator placement is associated with decreased procedure time for dilator insertion (from the time of speculum placement to the time of the last dilator placement).

      Hypothesis: Oral sedation will be associated with a decrease in time for the dilator insertion procedure compared to placebo.
   c. To evaluate whether oral sedation for cervical dilator placement is associated with increased success with inserting intended number of dilators (or more than intended) (as determined by a standardized algorithm).

      Hypothesis: Oral sedation will be associated with an increase in success with inserting the intended number of dilators (or more than intended) compared to placebo."
3. Descriptive objective: To describe dilator pain experience between the time of dilator insertion and the time of D&E.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Background: Few studies have examined pain management specifically during cervical dilator placement. One study found that intrauterine lidocaine (5cc of 2% lidocaine) combined with paracervical block did not improve pain control during laminaria insertion when compared with paracervical block and saline placebo.[3] Another study found that a paracervical block (18 ccs of 1% lidocaine) compared to sham cervical block was effective in reducing pain after laminaria placement.[7]

No prior studies have examined the effect of oral sedation on pain during cervical dilator placement. However, intravenous and oral sedation have been studied for pain management in the setting of surgical first and second trimester abortions. Regimens typically involve a combination of a benzodiazepine and an opiate medication.[8-10] One prior study of women undergoing first trimester surgical abortions reported that women who received IV sedation prior to the procedure had lower pain scores compared to woman who received only local anesthesia.[10] One study examining first trimester abortion found a small reduction in anxiety scores with the use of 1 mg oral lorazepam as compared to placebo, but no reduction in pain.[11]

Experience: The division of Family Planning at Johns Hopkins has executed numerous prior clinical research projects including randomized clinical trials. The PI and other listed physician investigators all have experience with studies with a variety of methodologies and are experienced in performing the

cervical dilator placement procedure. Additionally, we have discussed this project with our pharmacy department and they have the ability to create our desired placebos.

We also have the support of a dedicated research coordinator, nursing staff familiar with conducting clinical trials, and statistical support from BeadCORE.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

This will be a randomized, double- blind, placebo-controlled trial. We chose a randomized controlled trial as the study design given it is the gold standard for evaluating an intervention's effectiveness. This trial will be done with adherence to the SPIRIT and CONSORT guidelines for clinical trials.[12-13] The proposed randomized controlled trial will involve 2 arms.

It should be noted that individuals engaged in the research involving a particular patient will have no part in any decision as to the timing, method, or procedures used to terminate a pregnancy for that particular patient. (Please see details in study methodology below.)

Study methodology for this study will proceed as follows:

1. Eligible women between 17w0d and 23w6d gestational age (GA) presenting for cervical dilator placement prior to their D&E procedure who arrive with a support person will be approached regarding the study prior to dilator placement. We will be recording in a tally (no PHI information) how many patients meet our gestational age criteria, ,how many agree to hearing about the study the day of the study visit, and of those, how many meet full eligibility criteria After discussing the study with the study team, those who decline or are ineligible to participate will be tallied. We will also record the gestational age, main reasons for declining or main reasons for ineligibility (no PHI information). These tallies and information will be recorded in an excel file on a secure server or REDCAP. Informed consent will be obtained if the patient agrees to participate (see Written Consent in Section 15 of IRB application).
    a. The consent process will only take place once the patient has gone through pregnancy options counseling, and made the decision to proceed with the procedure and signed the appropriate consent forms for the abortion procedure. As such, the research study will not interfere with their decision to terminate their pregnancy or impact the timing, method, or procedures by which termination will be performed.

    A test text message will be sent to the patient's cell phone, confirming their phone works with our SMS system. We will ensure through the consent that subjects are encouraged to have security features enabled on their phone to prevent their text messages from being read by others.
2. We will collect survey data via tablet device on the subject's sociodemographic characteristics and pertinent medical history. (see Section 20, Supplemental Study Documents: Supplemental Survey/Assessments) We will record baseline pain prior to any medication administration.
    a. Survey data to be collected: participant's age, race/ethnicity, level of education, pertinent gynecological history, medical and mental health history, benzodiazepine and opiate use,

current medications, tobacco use, alcohol use, drug use, and history of intimate partner violence. EMR data to be collected: BMI data, obstetric history, prior abortion history, details regarding whether this pregnancy is a desired but anomalous fetus (all details that are routinely recorded as part of the documentation for the dilator visit).

3. Subjects in both arms will receive our institution's current standard pre-procedure analgesia for cervical dilator placement: oral ibuprofen (600 mg given 30 minutes prior to the procedure). In addition to this standard regimen, subjects will be randomized to receive either: (1) a dose of two oral sublingual pills, or (2) 1mg of oral lorazepam with 5 mg of oral oxycodone given 45-60 minutes prior to the start of the procedure.
   a. The subject, provider, and nursing staff will be blinded to the intervention. Our pharmacy will prepare the treatment drugs and placebos. Two research staff members will review and sign off verifying that drug or placebo has been provided correctly based on randomization. Following this, they will perform and document a cycle count of each investigational product for this study. Randomization will be stratified by gestational age (>= 20 weeks or <20 weeks) and the randomization allocation sequence will be computer-generated with a random number generator by a statistician. Our research assistant will be aware of the assignment and the physician who orders the study drug (oral sedation or placebo) will not be the same physician involved in the timing, method, or procedures of the patient's pregnancy termination that day. Additionally, our research coordinator who is engaging in the research activities with the patient will not be involved in any decision as to the timing, method, or procedures used to terminate the patient's pregnancy.
4. The primary outcome of interest, pain score, will be recorded via tablet device on a 100 mm visual analog scale (0 mm= no pain, 100 mm= worst pain possible) <u>after the last dilator is placed</u>. Secondary outcomes will be pain levels measured at seven other time points: (1) baseline before medication, (2) baseline after medication, (3) speculum placement, (4) tenaculum placement, (5) after paracervical block, (6) after first dilator placed, and (7) 15 minutes after the last dilator is placed. The cervical dilator procedure will otherwise be routine.
   a. Paracervical block: Subjects will receive the standard procedural analgesia paracervical block involving 20 ccs of 1% lidocaine prior to cervical dilator placement
   b. We will allow attendings, fellows, and residents to take part in cervical dilator placement as per routine, and our research assistant will record the level of training of the provider who inserts the majority of the dilators. None of these physicians taking care of an individual patient will be involved in the research procedures of ordering the study drug.
   c. We will be measuring time from speculum placement until last dilator placement. The provider will also be asked regarding the ease of dilator placement after the last dilator has been placed.
5. Additional outcomes to be assessed via tablet device will be symptoms (nausea, vomiting, dizziness, drowsiness, etc.) experienced by subjects as reported 15 minutes after dilator placement. (see Section 20, Supplemental Study Documents: Supplemental Survey/Assessments). We will extract data from the subject's chart regarding number of dilators placed and the adverse events that occurred during the dilator placement visit (syncope or vasovagal reaction, cervical laceration, respiratory depression, etc.) after the visit. (see Section 20, Supplemental Study Documents: EMR data to be obtained). If the intended number (or more than intended number) of dilators is placed that will be considered a success in placing the intended number of dilators and if less than the intended number of dilators is placed that will be considered a non-success in placing the intended number of dilators.
6. Women will be discharged home with standard prescriptions for ibuprofen 800 mg and oxycodone 5 mg to take as needed.

7. Participants will be contacted via text message at 2, 4, and 8 hours after dilator insertion

a. Text messages will originate from a password protected study cell phone. The Android application "SMS Scheduler" will be used to send standardized text messages to the participant at pre-programed time intervals from time of dilator insertion.
b. Text messages content:
    i. Current Numeric Rating Scale (NRS) pain score
    ii. Inventory of analgesic use since last contact
    iii. Presence of symptoms

8. Upon admission prior to D&E, we will document the time and assess the current NRS pain score, additional analgesic use since 8-hour text message contact, and presence of symptoms.
9. Subjects will be financially compensated (with a $100 gift card and parking voucher the day of their D&E) for study participation after presenting for their D&E. They and their support person will also receive a $6 meal voucher. They will be compensated an additional $5 for each completed text message contact (at 2,4, and 8 hours).

Approach of potential subjects: We will introduce the study via telephone during their routine cervical dilator appointment intake call prior to their visit. (see Section 13, Part 7: Telephone screening script) We will keep a log tally (no PHI information recorded) of the number of those who agreed to hear more about the study and those who did not. We are introducing the study via telephone because enrollment in the study will require that subjects have someone to escort them home (support person) and we do not want women to be ineligible if they desire to be in the study but they fail to bring a support person the day of their cervical dilator appointment. Our clinic nurse will briefly introduce the study and the need to bring a support person if the patient wants to be eligible. The consent for the study will be conducted at the time of the clinical visit for cervical dilator placement and after the patient decision regarding termination has been made and after surgical consents for the abortion procedure have been signed.

The proposed research will require the use of hospital EMR to ensure we capture all side effects/symptoms and adverse events and to also assess the number of dilators placed by the physician. We are requesting access to EMR in our IRB protocol.

b. Study duration and number of study visits required of research participants.

Our primary aim is to be able to detect a clinically significant difference in pain after the last dilator is placed. Given a review of prior literature addressing pain during procedures that involve the cervix (i.e. IUD insertion, 1st trimester abortion) in addition to our calculations, we have determined 60 subjects will be needed to adequately power the study.

Given that we see 15 women who would meet inclusion criteria per month, we expect overall length of enrollment to be approximately 8 months, accounting for a 50% non-enrollment rate. Study visits required of participants involve the cervical dilator placement visit and the visit for their following D&E procedure the next day, both of which are routine for women undergoing 2nd trimester abortion.

We received IRB approval and our grant award. We anticipate enrollment to extend from July 2017 until August 2018 when we will reach our sample size. We anticipate data cleaning and analysis to take from August 2018-September 2018 with the help of our consultants at BeadCORE. Report writing will take place from September to October 2018. In summary, we will start enrollment July 2017 and our goal end date will be August 30, 2018.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

The subject, provider, and nursing staff will be blinded to the intervention. Our pharmacy will prepare the treatment drugs and placebos. Randomization will be stratified by gestational age (>= 20 weeks or <20 weeks) and the randomization allocation sequence will be computer-generated with a random number generator by a statistician. Our research assistant will be aware of the assignment and pass the treatment drugs on to the nursing staff who will administer the drugs to the subject.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Patients will receive routine care with the addition of being randomized to receive either: (1) a dose of two oral placebo pills, or (2) 1mg of oral lorazepam with 5 mg of oral oxycodone given 45-60 minutes prior to the procedure. No current therapy will be stopped.

e. Justification for inclusion of a placebo or non-treatment group.

No prior studies have examined the effect of oral sedation on pain during cervical dilator placement. Most patients currently undergo this procedure without oral sedation. Thus, there is no current evidence regarding whether the provision of oral sedation for cervical dilator placement will improve pain during the procedure. A placebo is justified in this setting of clinical equipoise.

f. Definition of treatment failure or participant removal criteria.

In our study there is no treatment failure situation as we do not anticipate a certain result with either study arm. Study discontinuation (participant removal) will occur when a subject takes the study drug but then declines or is unable to proceed with cervical dilator placement. Subjects may also request to discontinue at any time.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

The patients will only be receiving the study therapy/intervention during their cervical dilator visit. The end of the study is when they complete their D&E procedure. For subjects that do not follow up for their D&E the day following their cervical dilator placement (an extremely rare occurrence), we will follow our clinic protocol regarding contacting the subject. Subjects lost to follow up will be included in the primary outcome analysis.

Any subjects who discontinue the study or do not follow up on the day of their D&E will be analyzed using intention to treat analysis.

5. Inclusion/Exclusion Criteria

Inclusion criteria: To be eligible for the study, women must be aged 18-50 years, English speaking, with an intrauterine pregnancy (either viable or non-viable) between the gestational ages of 17w0d and 23w6d presenting for cervical dilator placement prior to their D&E procedure. They must have a support person present with them at the time of their dilator placement.

1. We will not enroll non- English speaking participants, however we will allow a participant who has a hearing impairment to be consented if they can read English and if they have an American Sign Language interpreter to assist in the consent process and study participation.
2. For the exploratory objective, they must have cell phone that is capable of text messaging. This will be tested upon enrollment. If they do not have a cell phone, they will still be eligible for the main study, and if enrolled, will be excluded from steps 7 and 8 of the study methodology as described in the Study Procedures section.

Exclusion criteria: Women will be excluded if they are non-English-speaking, are taking a daily benzodiazepine or opiate, or have a known allergy or contraindication to NSAIDs, opiates, or benzodiazepines. We feel it is important to exclude women who are taking a daily benzodiazepine or opiate as they will likely have tolerance to the intervention drugs at our selected study doses and respond differently from other women.

6. Drugs/ Substances/ Devices
    a. The rationale for choosing the drug and dose or for choosing the device to be used. We choose the intervention drugs lorazepam and oxycodone because sedation regimens previously studied for pain management in the setting of surgical first and second trimester abortions typically involve a combination of a benzodiazepine and an opiate medication.[8-10]

We chose the drug doses to be 1 mg of lorazepam and 5 mg of oxycodone to minimize the possibility that subjects would feel very symptomatic or lethargic (anecdotally we have seen this happen to lower weight patients (BMI<25kg/m2) in clinic taking a combination of 2 mg of lorazepam and 10 mg of oxycodone). We discussed with our research pharmacy team the utility of studying a 2 mg lorazepam dose in the setting of increased BMI, however per their recommendations there is little evidence to support an increased dose for increased BMI.

    b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed. N/A
    c. Justification and safety information if non-FDA approved drugs without an IND will be administered. N/A

7. Study Statistics
    a. Primary outcome variable.

The primary outcome of interest, pain score, will be measured via tablet device on a 100 mm visual analog scale (0 mm= no pain, 100 mm= worst pain possible) after the last dilator is placed.

    b. Secondary outcome variables.

Secondary outcomes will be pain levels measured at seven other time points: (1) baseline before medication, (2) baseline after medication, (3) speculum placement, (4) tenaculum placement, (5) after paracervical block, (6) after first dilator placed, and (7) 15 minutes after the last dilator is placed. The cervical dilator procedure will otherwise be routine.

Additional outcomes to be assessed via tablet device will be symptoms (nausea, vomiting, dizziness, drowsiness, etc.) experienced by subjects as reported 15 minutes after dilator placement. We will extract data from the subject's chart regarding number of dilators placed and the adverse events that occurred during the dilator placement visit (syncope or vasovagal reaction, cervical laceration, respiratory depression, etc.) after the visit.

As part of our exploratory objective we will also be looking at the additional outcomes pain, analgesic use, and presence of symptoms 2,4, and 8 hours after dilator insertion.

    c. Statistical plan including sample size justification and interim data analysis.

Our primary aim is to be able to detect a clinically significant difference in pain after the last dilator is placed. Given a review of prior literature addressing pain during procedures that involve the cervix (i.e.

IUD insertion, 1st trimester abortion) in addition to our calculations, we have determined 60 subjects will be needed to adequately power the study to detect a clinically significant difference in visual analog pain scores of 20 mm[6] at a given instance and obtain 80% power with a 5% alpha error rate. This plan was formulated with our consultants at BeadCORE.

Given our small sample size we will perform our interim data analysis when we have data from 75% of our sample size.

d. Early stopping rules.

If we find the adverse event rate to be significant ($p<0.05$) in our intervention arm (at the time of interim analysis) we will consider stopping the study early.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

There are risks to taking oral sedation including lethargy, syncope, and respiratory depression. We chose the intervention drug doses to be 1 mg of lorazepam and 5 mg of oxycodone to minimize the possibility that subjects would feel very symptomatic or lethargic. We will have a trained nurse administering the drug to the patient and with the patient during the entirety of the cervical dilator placement. The patient will recover in the waiting room where a nurse and physician will be readily accessible to assess and address any side effects that the subject may have to the oral sedation. This is the standard clinical care that is currently practiced in the clinic.

There are no additional procedures expected with the cervical dilator placement visit.

b. Steps taken to minimize the risks.

See part a.

c. Plan for reporting unanticipated problems or study deviations.

Any unanticipated problems or study deviations will be immediately reported to our research coordinator and subsequently evaluated with the PI. If necessary, problems that lead to protocol change or study deviations will be reported to the IRB.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

There is a possibility for breach of confidentiality if protected health information that is identifiable is not protected. To prevent this, REDCap data (all the data collected at cervical dilator visit) will be password protected, and stored on the secure web application.

All other data will be de-identified and stored on a secure server within the university. Any hard copies of data (i.e. consents) will be stored in a locked file cabinet inside a locked office within the university.

There is also a potential for breach of confidentiality during the text message portion of the study. Prior to first text message, the research assistant will program the participant into the phone contact list with their study number and preferred phone number. Text message responses will be input into the study database on REDCap on a weekly basis and the participant's contact information and text messages deleted from the phone. Special attention will be paid to ensuring participant privacy as communication is undertaken with

them (no text messages will use the words “pregnancy” or “abortion”) while they are at home and potentially around others not aware of their pregnancy or abortion decision. We will ensure through the consent that subjects are encouraged to have security features enabled on their phone to prevent their text messages from being read by others. We have also confirmed that the text messaging application does not use a cloud storage for text messaging data; it is unlikely that text messages would be accessed by anyone but the sender and receiver. Though it is likely that the text messages are encrypted, we have included additional detail regarding the risks of unencrypted data in our informed consent. We have received written approval from Darren Lacey, Chief Information Security Officer, regarding the use of the text messaging application in our study.

e. Financial risks to the participants.

The only possible financial risk to the participant is if they have a per-text messaging fee associated with their phone service. In these situations, participants will be compensated for text messaging fees related to the study.

9. Benefits
   a. Description of the probable benefits for the participant and for society.

Participant benefits: The participant may find a benefit of decreased pain during and after the procedure if they are assigned the treatment drug arm. They will also be financially compensated for participating in the study, see above and also reiterated in next section.

Society benefits: Findings from this study could help improve approaches to second trimester D&E cervical preparation, addressing a 2016 Fellowship in Family Planning Research Priority. Minimal literature currently exists regarding pain management specifically during dilator placement. There is no data regarding the dosage of benzodiazepines or opiate medications that are effective for pain management during dilator placement. This study would also add to limited data regarding baseline pain during dilator placement and the pain course after dilator placement. From our experiences in running the study, we hope to develop a standardized clinic protocol for those who desire oral sedation for dilator placement.

10. Payment and Remuneration
    a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Subjects will be financially compensated (with a $100 gift card and parking voucher the day of their D&E) for study participation after presenting for their D&E or immediately after their dilator placement visit if they are not participating in the text messaging portion of the study. They and their support person will also receive a meal voucher (value $6 each). They will be compensated an additional $5 bonus for each completed text message contact (at 2,4, and 8 hours). Thus, they can be compensated a maximum of $115 if they complete all parts of the study.

The participants must show up the next day for their D&E to be compensated for the text messaging portion of the study (this is stated in the consent). Thus, if they do not show up for their D&E they will not have completed the protocol and will not be compensated for the text messaging portion (not presenting for D&E is extremely rare). There are no reductions or penalties otherwise.

11. Costs
    a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There will be no additional cost to the patients beyond what is routine for the cervical dilator visit and D&E.

The study drugs (both placebo and oral sedation drugs) will be covered with a grant from the Society of Family Planning. Text messaging fees (if they apply to participants' phone plans) will be covered by the same grant.

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