Self-administered lidocaine gel for pain-control during cervical preparation for dilation and evacuation: A randomized controlled trial

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Background

Methods of cervical preparation prior to dilation and evacuation (D&E) after 16 weeks gestation vary. Most commonly, providers in the United States use misoprostol, mifepristone, osmotic dilators, and laminaria—either independently or in conjunction with each other. Efforts to research the use of mifepristone and misoprostol alone for cervical preparation are motivated by the desire to decrease discomfort associated with cervical preparation and increase access to abortion at later gestations by eliminating the use of laminaria or osmotic dilators. To compliment these efforts, more research is needed to investigate methods of pain control for cervical preparation with osmotic dilators and laminaria to decrease patient discomfort. Women report laminaria and osmotic dilator placement to be painful.

Pain control trials in the abortion literature often focus on pain with the abortion procedure itself. Those studies that report on pain with osmotic dilators show that insertion is painful. Few studies have focused on the methods of pain control for laminaria or osmotic dilator insertion alone. A recent study showed that paracervical block reduced pain with osmotic dilator insertion compared to a sham block [Soon R, et al abstract SFP). Self-administered lidocaine gel is a method of pain control found to be no worse than a paracervical block for pain control during surgical abortion at gestations of less than 12 weeks. We hypothesize that self-administered lidocaine gel is no worse than paracervical block for pain control with cervical preparation.

This study seeks to compare self-administered lidocaine gel for pain control during cervical preparation (laminaria and/or osmotic dilator insertion) for D&E to paracervical block.

Objectives

Primary Objective

Pain perceived at the time of dilator insertion measured by Visual Analogue Scale (VAS) (0-100mm).

Secondary Objectives

- Pain perceived at additional time points before, during, and after the procedure (all measured by VAS (0-100mm):
    - Anticipated Pain: 30 minutes prior to procedure
    - Baseline Pain: Immediately prior to procedure
    - Dilator Insertion: Immediately following dilator insertion
    - Post-Procedure Pain: 10-15 minutes following procedure
    - Overall Pain: Assessed after procedure
- Incidence of complications
- Provider reported ease of insertion

- Global satisfaction (acceptability) of procedure

Study Drugs

Experimental Group:
Xylocaine (lidocaine HCl) is a common local anesthetic that works by stabilizing the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses. Local anesthetics of the amide type are thought to act within the sodium channels of the nerve membrane. According to the packaging insert, anesthesia is achieved within 5 minutes, depending on the area of application, and duration of anesthesia is approximately 20-30 minutes. It is used prior to many genitourinary procedures involving mucus membranes including the urethra, anus, and vulva. While no recommended dose is known for vaginal use prior to surgical abortion, recommended doses are known for the following procedures: 20 ml for proctoscopy/anoscopy; 10 ml for female urethral anesthesia as in cystoscopy. A single maximum dosage for 2% Xylocaine jelly is not established [Blanco 1982], however Lexicomp drug information for topical lidocaine jelly cites a maximum dose of 600 mg in any 12-hour period.

The serum toxicity of intracervical lidocaine is thought to be around 5 ug/ml [Blanco 1982] and a study looking at serum lidocaine levels 10 minutes after paracervical injection of 20 ml of 1% lidocaine (200 mg total) found mean blood levels of 0.9 to 1.61 ug/ml [McKenzie 1978].

Similarly, a study investigating vaginal anesthesia with 4ml of 10% lidocaine spray (400mg total) 5 minutes prior to high dose intracavitary brachytherapy found a significant decrease in procedural pain [Chen 1998]. This study also looked at serum lidocaine levels at various time points following administration and found that the 400mg dose never reached toxic levels in participants. These data are further supported by non-toxic levels seen after nasopharyngeal and oropharyngeal application in the studies sited above.

Based on this information, participants in the lidocaine gel group will self-administer 20 ml of 2% lidocaine HCl vaginally (400 mg total) 20-30 minutes prior to the start of the procedure. We are allowing a window of time to account for real life clinic practice and possible delays.

The product:
- XYLOCAINE® JELLY 2% (lidocaine hydrochloride) AstraZeneca
    - 20 mL (20 mg/mL) – 400mg total

Control Group:
Paracervical block technique:
- Syringe loaded with 12 mL of 1% lidocaine (120 mg); 22-gauge spinal needle (x mg total)

- 2 mL injected at the tenaculum site, either 6 or 12 o'clock superficially into the cervix
- The tenaculum is immediately placed at the previously injected site
- The remaining 10 mL are slowly injected into the cervicovaginal junction in two equal aliquots at 4 and 8 o'clock; the injection is continuous from superficial to deep (1-2 cm) to superficial (injecting with insertion and withdrawal)

Study Population
Women presenting for abortion ≥16 weeks gestation will be invited to participate in the study protocol. This population was selected, as they typically require more dilators than the patients at lower gestational ages.

Explanation of Sample Size
Studies of patient reported pain scores indicate that the minimum, significant difference in pain score on a 100mm Visual Analogue Scale (VAS) is 13-16mm. Studies of laminaria insertion document pain scores ranging from 43-70mm, with standard deviation of 22-23. We determined Considering the continuous primary outcome and our non-inferiority hypothesis, if there is truly no difference between paracervical block and self-administered lidocaine gel for pain control with cervical preparation for D&E after 16 weeks gestation, 68 participants are required to be 80% sure that the lower limit of a one-sided 97.5% confidence interval (or equivalently a 95% two-sided confidence interval) will be above the non-inferiority limit of 15mm. Accounting for participant drop-out, we will recruit 72 women to participate in this study (significance level, alpha of 2.5%; power of 80%; standard deviation of 22; non-inferiority limit of 15).

Overview of Study Design

Recruitment and Allocation of Subjects
Subjects will be recruited from the Stanford Gynecology Clinic in Palo Alto, California. They will be identified for participation through prospective chart review. Informed consent will be obtained from a trained research coordinator. Upon agreeing to participant, subjects will be randomized through block randomization to a study arm.

Criteria for Subject Selection
Inclusion:
- Women 18 and older
- Intrauterine pregnancy ≥16 weeks gestation
- English speaking competency
- Willing and able to sign consent forms
- Agree to comply with study procedures

Exclusion:
- Women less than 18 years of age

- IV conscious sedation
- Known allergy to study medication (lidocaine)
- Any women not meeting inclusion criteria above will be excluded from participation

Study Procedures

This study will take place during subjects' cervical preparation visit. Following informed consent, participants will be randomized to a study group—group allocation information will be kept in a sealed, opaque envelope. Upon consenting for the study, a research coordinator will assign a unique subject ID number to the participant. This subject ID number's envelope will be opened to determine allocation. Participants, research staff, and health care provider will not be blinded to the allocation.

If the subject is randomized to the experimental group (self-administered lidocaine gel), she will be instructed on how to self-administer the gel vaginally by the study coordinator. She will insert 20ml of 2% lidocaine gel into her vagina using a pre-loaded syringe. After 15 minutes, the procedure will be begin.

If the subject is randomized to the control group (provider-administered paracervical block), cervical anesthesia and preparation will commence to standard.

For both groups, the research coordinator will collect demographic and medical history and document procedure data. For VAS scores, the research coordinator will administer the 100mm VAS on an iPad. Pain scores will taken "in real time". There is no follow-up for this study.

Data Collection

Data collection will be obtained through a REDCap survey.

Data to be collected include:

- Demographics
    - Location of procedure
    - MRN
    - Date enrolled
    - First name
    - Last name
    - Date of birth
    - Age
    - Phone number
    - Race
    - Ethnicity
- Medical History (Physical Exam and Ob/Gyn History)
    - Height
    - Weight

    - BMI
    - Gestational age
    - Medication allergies
    - Current medications
    - Number of previous pregnancies
        - Number of previous vaginal deliveries
        - Number of previous cesarean sections
        - Number of previous abortions
        - Number of previous abortions after 16 weeks gestation
        - Number of miscarriages
    - Medical problems
    - Previous surgeries
        - Previous cervical surgeries
- Procedure Data
    - Provider type (i.e. resident, fellow, attending)
    - Provider reported ease of procedure
    - Uterine position
    - Initial cervical dilation
    - Number of osmotic dilators or laminaria placed
    - Time with lidocaine gel before tenaculum
    - Time with paracervical block before tenaculum
    - Total speculum time
    - Complications
- Procedure VAS Data
    - Anticipated
    - Baseline
    - Speculum insertion
    - Paracervical block (control group only)
    - Tenaculum placement
    - Laminaria/osmotic dilator insertion
    - Post-procedure
    - Overall pain
- Acceptability Data
    - Gel leakage acceptability (experimental group only)
    - Likelihood to recommend procedure
    - Comfort with tampons
    - Maximum time willing to wait for pain control

Data Analysis and Monitoring
Enrollment will be reviewed bi-weekly by the research team. Given that there are minimal safety risks involved in this study, we do not plan to convene an independent Data Safety Monitoring Board (DSMB).

Data Management and Storage
Data will be entered into and stored on REDCap.

Methods of Analysis
Data will be exported from REDCap to SPSS Version 23.0 for analysis.

Perioperative characteristics will be examined among the groups using chi square test and fisher's exact test, where appropriate; mean and median VAS pain scores will be analyzed with Student's *t*-tests and non-parametric tests, respectively; mean and median overall satisfaction with pain control and provider reported ease of procedure via VAS scores will be compared using Student's *t*-tests and non-parametric tests, respectively; linear regression will be completed in multivariable analysis to identify predictors of pain.

Analysis and Dissemination of Results
Analysis will occur upon completion of study enrollment. The co-investigators plan to prepare at least one manuscript for submission to a peer-reviewed journal. In addition, the co-investigators will present the results of the study at conferences and meetings where appropriate.

Risks and Benefits
Participants are not promised any benefits from participating in the study.

Potential risks associated with this study are minimal. The risk to the participants' physical, psychological, economic, or social well-being in this study is not anticipated to be any different or greater from women not participating in the study.

The risks, side effects, and discomforts of the study, whether the subject receives lidocaine gel or lidocaine paracervical block, are expected to be similar and include:

- Side effects with medications
    - Lidocaine - with numbing medicine in a woman's cervix, there is an infrequent risk of getting a unusual taste in the woman's mouth, ringing in her ears, nausea or light-headedness. Rarely, a person can have a seizure from the numbing medicine.
- Pelvic examination: Subjects may infrequently experience some discomfort during the pelvic exams
- Emotional Discomfort: Some of the questions the subject will be asked in this study may make the subject feel uncomfortable or embarrassed. She can refuse to answer any question that makes her uncomfortable or embarrassed, from any person, at any time.

Cost to the Participant and Compensation for Participation
Participants will not be compensated for their time of participation in this study. There will be no additional cost for participation in the study.