12 vs. 20 mL paracervical block for pain-control during cervical preparation for dilation and evacuation: A single-blinded randomized controlled trial

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Project Summary

Description of the Project

1.1 Rationale and objectives of the study

1.1.1 Rationale

Paracervical block (PCB) is a widely used, but largely unstandardized technique for pain management in gynecological procedures. From hysteroscopy to first trimester abortion procedures to dilator placement for dilation and evacuation, providers utilize the paracervical block to manage cervical dilation pain. However for such a widely used technique, the exact method is often provider or site specific. A 2009 survey of National Abortion Federation members [i] illustrates that the volume alone of anesthestic used for PCB in first trimester abortion procedures varies tremendously amongst providers. That said, research published over the last few years has had enormous impact on global guidelines, such as those published by Ipas. New techniques for paracervical block that focus on limiting symptoms and resources while also ensuring adequate pain management are needed to improve care for women around the world.

A randomized controlled trial done by Renner et al. in 2012[ii] demonstrated that a 4-site, 18 mL 1% lidocaine paracervical block, with a 2 mL injection for tenaculum placement, used during first-trimester surgical abortions was beneficial in reducing pain due to cervical dilation when compared to sham paracervical block. The block technique endorsed by Renner et al. was based on findings from a combination of studies about paracervical block that investigated variations in needle injection site[iii], type of lidocaine[iv], depth of lidocaine injection[v], general vs. local anesthesia[vi], and wait time between injection and procedure[vii]. Missing from consideration, however, was the *volume* of lidocaine necessary to achieve a reduction in dilation pain. The final technique used in Renner et al.'s study was as follows:

- Syringe loaded with 18 mL of 1% plain lidocaine buffered with 2 mL 8.4% sodium bicarbonate (20 mL total); 20-gauge spinal needle
- 2 mL injected at the tenaculum site, 12 o'clock superficially into the cervix
- The tenaculum is immediately placed at 12 o'clock
- The remaining 18 mL are injected slowly over 60 seconds into the cervicovaginal junction in four equal aliquots at 2, 4, 8, and 10 o'clock; the injection is continuous from superficial to deep (3 cm) to superficial (injecting with insertion and withdrawal)
- Dilation begins 3 minutes after application of the block

A subsequent study done by Renner et al. in 2016[viii] aimed to further refine this technique and looked at both the 3-minute wait time and the use of 4-site versus 2-site injection. Results of the study were largely inconclusive, suggesting that no wait time is no worse than a three-minute wait and that 2-site and 4-site injections may be interchangeable. Despite these findings, global guidelines and provider preference continue to follow findings from Renner et al.'s 2012 study.

As the dangers of lidocaine injection are minimal, but not absent, and the administration of a paracervical block is painful and time-consuming, we propose comparing a technique similar to

the one put forth by Renner et al. with one that has been used in multiple Stanford studies and notably employs a smaller volume of lidocaine and only two injection sites. The technique is as follows:

- Syringe loaded with 12 mL of 1% lidocaine (120 mg); 22-gauge spinal needle
- 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 (3 cm) to superficial (injecting with insertion and withdrawal)
- No wait time between injection and dilator insertion

We aim to compare this technique with one similar to Renner et al.'s technique from 2016:

- Syringe loaded with 20 mL of 1% lidocaine (120 mg); 22-gauge spinal needle
- 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 18 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 (3 cm) to superficial (injecting with insertion and withdrawal)
- No wait time between injection and dilator insertion

Our justification for this proposed technique comparison is as follows:

With regards to smaller dosage, there is much research to be done. While the lidocaine label recommends a maximum dose of 200 mg (20 mL at 1%) of lidocaine per 90-minute period for paracervical block,[ix] it does not recommend a minimum dose. Renner et al.'s 2012 study[ii] provides evidence for paracervical block over sham for cervical dilation pain and Chanrachakul's 2001 study[x] provides evidence that pain relief comes from both lidocaine and distention rather than distention alone. These studies point to the benefit of using lidocaine, but to date there is little data providing the optimal dose between 0 mL and 20 mL. With this knowledge, we propose the use of 10 mL of lidocaine in order to maintain the use of lidocaine for pain control, but minimize symptoms (such as metallic taste, ringing in the ears, and at worst, seizure or cardiac arrest) that are more likely to manifest with 20 mL.

With regards to 2-site versus 4-site, our aim is to build on the findings from Glantz and Shomento's 2001 study and Renner et al.'s 2016 study. Glantz and Shomento's study from 2001[iii] contained four study arms and looked at both 1% chloroprocaine versus placebo and 4-site versus 2-site injection. While the original paper concluded that PCB with chloroprocaine provides more pain relief than saline for both 4-site and 2-site injections, subsequent reanalysis from 2009[xi] showcased that preference for 4-site or 2-site versus saline depended on the time point at which pain was measured. Regardless, more importantly, the findings showed that when comparing 4-site 1% chloroprocaine block to 2-site 1% chloroprocaine block, there is no statistical difference. Furthermore, Renner et al.'s 2016 study[viii], which compared 20 mL of 1% buffered lidocaine at 4-site versus 2-site, showcased that using noninferiority analysis, there is no statistical difference between 4-site and 2-site block. Additionally, while superiority analysis demonstrated that 4-site is stastically superior to 2-site for pain control at cervical dilation, this

demonstrated difference is not clinically significant. All in all, these data point toward the clinical conclusion that 2-site may be utilized in place of 4-site. Our proposed technique follow findings from these studies and if proven effective, would result in fewer painful injections during paracervical block.

Concerning depth of injection, we will utilize the 3 cm depth as used in Renner's studies. Wiebe et al.'s 1992 study[iv] and Cetin and Cetin's 1997 study[v] suggest utilizing deep injection, as dilation pain scores were lower for deep injection in both studies.

Phair et al.'s 2002 study[xii] and Renner et al.'s 2016 study[viii] both showcased that there is no significant difference in pain with cervical dilation when comparing no-wait between PCB injection and cervical dilation to wait. As such, we have opted to exclude a wait time.

With regard to plain lidocaine versus buffered lidocaine, while several studies have showcased the benefit of utilizing buffered lidocaine instead of plain lidocaine[iv], given the high cost and prolonged preparation time associated with creation of a buffered lidocaine solution, we have decided to use 1% plain lidocaine. Our hope is that by showcasing pain control with a more cost-effective anesthetic, our results will be generalizable to a larger global audience.

Finally, while many studies focus on pain control in first-trimester abortion, including Renner et al., in order to isolate cervical dilation pain from uterine pain, we have chosen to focus on the cervical preparation procedure needed prior to a second trimester surgical abortion rather than the surgical procedure itself. Need for additional research in this timeframe was highlighted in Soon et al.'s[xiii] work, which demonstrated that the paracervical block technique utilized by Renner et al. was effective in reducing pain associated with osmotic dilator insertion prior to second trimester abortion. We also believe that isolating the pain of the cervical dilation procedure will allow us to generalize the findings of our study to be meaningful for any procedure in which cervical dilation is necessary.

1.1.2 Objectives and hypothesis

We hypothesize that a 2-site, 12 mL 1% plain lidocaine injection paracervical block (PCB) technique (2 mL for tenaculum placement, 10 mL for paracervical block) will provide non-inferior pain control compared to a previously established 2-site, 20 mL 1% lidocaine injection PCB (2 mL for tenaculum placement, 18 mL for paracervical block) when administered for dilation pain control during cervical preparation.

Our primary objective is to determine pain perceived at time of dilator insertion measured by Visual Analogue Scale (VAS; Dilator Insertion: Immediately following dilator insertion) (0-100mm).

Secondary objectives include assessing:

- Pain perceived at additional time points before, during, and after the procedure (all measured by VAS (0-100mm; 0 being no pain and 100 being worst pain imaginable):
    - Anticipated Pain: 30 minutes prior to procedure

    - Baseline Pain: Immediately prior to procedure
    - Block injection Pain: Immediately following injection, but prior to dilator insertion
    - Post-procedure Pain: 10-15 minutes following procedure
    - Overall Pain: Assessed after procedure (prior to discharge)
- Total procedure time, as defined by speculum time
- Incidence of complications
    - Inability to dilate cervix
    - Seizure
    - Cardiac arrest
    - Structural trauma (uterine perforation, cervical laceration, etc.)
    - Hemorrage (EBL estimation)
- Symptom Data
    - Following block injection, any experience of:
        - Metallic taste in mouth
        - Ringing in ears
        - Lightheadedness
- Any other systemic symptoms experienced, including vasovagal reaction
- Provider reported ease of insertion
- Global satisfaction (acceptability) of procedure reported by participant (VAS, 0-100mm; 0 being unsatisfied and 100 being fully satisfied)

1.2 Design and methodology

1.2.1 Research design and General Methodological Approach

This is a non-inferiority, single blinded, randomized controlled trial.

1.2.2 Criteria for the selection of subjects

Women who need dilator placement for second trimester D&E procedures will be invited to participate in the study protocol. This population was chosen because our aim is to isolate how best to manage cervical dilation pain and not uterine aspiration pain, which is potentially a confounding factor when analyzing pain perceived during first trimester abortions rather than cervical dilation procedures alone. Additionally, we will limit our study population to those women presenting for an abortion ≥16 weeks gestation. This population was selected as they typically require more dilators than the patients at lower gestational ages.

Specific inclusion criteria:

- 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

1.2.3 Subject recruitment and allocation

Subjects will be recruited from Stanford Gynecology Clinic in Palo Alto, California and at Planned Parenthood Mar Monte in San Jose, CA.

- At Stanford, potential participants will be identified by prospective chart review done by clinical research coordinators. Once identified, clinical research coordinators will obtain permission from provider to speak with participants.
- At Planned Parenthood, clinic staff will notify clinical research coordinators of potential participants.

To ensure even allocation across sites, two randomization schemes will be created, one for each site.

1.2.4 Description of the drugs and devices to be studied

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.

For paracervical block the drug label recommends a maximum dose of 200 mg (100 mg per side) in a 90 minute period[ix]. Given risk of rapid systemic absorption and possible maternal seizure and cardiovascular collapse, the maximum dose should not be exceeded. The label also recommends slow injection and a 5-minute interval between each side.

Contraindications to lidocaine include the following:

- Hypersensitivity to lidocaine or any component of the formulation
- Hypersensitivity to another local anesthetic of the amide type
- Adam-Stokes syndrome
- Wolff-Parkinson-White syndrome
- Severe degrees of SA, AV, or intraventricular heart block (except in patients with a functioning artificial pacemaker)
- Premixed injection may contain corn-derived dextrose and its use is contraindicated in patients with allergy to corn or corn-related products

1.2.5 Admission procedure

Eligible women will be screened and identified in two ways. The first will be via prospective chart review done by Stanford clinical research personnel. The second will be providers and clinic staff informing clinical research personnel of potential participants.

If potential participants meet inclusion criteria and permission has been granted by their provider, they will be approached by a clinical research coordinator who will review the study protocol and obtain informed consent. After obtaining informed consent, participants will be randomized to a study arm via computer-generated block randomization using REDCap

software. The provider and staff will be aware of arm allocation, but participants will remain blinded.

There will be two study arms:

Experimental:

- Syringe loaded with 12 mL of 1% lidocaine (120 mg); 22-gauge spinal needle
- 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 (3 cm) to superficial (injecting with insertion and withdrawal)
- No wait time between injection and dilator insertion

Control:

- Syringe loaded with 20 mL of 1% lidocaine (120 mg); 22-gauge spinal needle
- 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 18 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 (3 cm) to superficial (injecting with insertion and withdrawal)
- No wait time between injection and dilator insertion

Prior to the procedure, clinical research coordinators will obtain the following baseline information using REDCap:

- 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
    - First day of lest menstrual period
    - Gestational age defined by U/S
    - 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
    - Recent deliveries
    - Medical problems
    - Previous surgeries
        - Previous cervical surgeries
        - Other previous surgeries

The participant will then be prepped for the procedure. At that point, the clinical research coordinator will accompany participants throughout the duration of their procedure and obtain the following information:

- Procedure Data
    - Provider type (i.e. resident, fellow, attending)
    - Provider reported ease of procedure
    - Initial cervical dilation
    - Uterine position
    - Number of osmotic dilators placed
    - Total procedure time, as defined by speculum time
    - Digoxin given
    - Complications
        - Inability to dilate cervix
        - Seizure
        - Cardiac arrest
        - Structural trauma (uterine perforation, cervical laceration, etc.)
        - Hemorrage (EBL estimation)
    - Administration of Mifepristone for cervical preparation
- Procedure VAS Data
    - Anticipated Pain: 30 minutes prior to procedure
    - Baseline Pain: Immediately prior to procedure
    - Block injection Pain: Immediately following injection, but prior to dilator insertion
    - Dilator Insertion Pain: Immediately following dilator insertion
    - Post-procedure Pain: 10-15 minutes following procedure
    - Overall Pain: Assessed after procedure (prior to discharge)
- Symptom Data
    - Following block injection, any experience of:
        - Metallic taste in mouth
        - Ringing in ears
        - Lightheadedness
    - Any other systemic symptoms experienced, including vasovagal reaction
- Acceptability Data
    - Global sastisfaction with procedure
- Recognition of group allocation

1.2.6 Follow-up procedure

No follow-up required.

1.2.7 Criteria for discontinuation

Participants requiring additional cervical anesthesia or intervention due to complication during the dilation procedure will be discontinued from the study.

1.2.8 Laboratory and other investigations

Not applicable.

1.2.9 Data management

Data will be collected on REDCap software, and will be coded, monitored and verified.

1.2.10 Data 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. Complications and patient symptoms associated with lidocaine toxicitiy will be examined between the groups using chi square test and fisher's exact test, where appropriate.

1.2.11 Number of subjects and statistical power

88 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 less than the non-inferiority limit of 15mm. Accounting for participant drop-out, we will recruit 96 women to participate in this study (significance level, alpha of 5%; power of 80%; standard deviation of 28; non-inferiority limit of 15).

1.2.12 Study limitations

The major limitation of this study is the inability to blind providers. Given the need to give different volumes of lidocaine, blinding is not possible.

1.2.13 Duration of project

Given that recruitment will take place at both Stanford and Planned Parenthood, we will assume a conservative recruitment rate of 11 participants per month which will require approximately 9 months.

1.3 Project management

Project management will be coordinated, conducted, and monitored primarily by [redacted], BA, protocol director. Co-investigators, [redacted], MD, MS, [redacted], MPH, [redacted], MD, and [redacted], MD, MPH will also monitor the study.

1.4 Links with other projects

Not applicable.

1.5 Main problems anticipated

Problems anticipated include difficulty recruiting participants and obtaining pain scores during procedure.

Difficulty recruiting participants: Given participants agreeing to participate in the study may be randomized to a smaller dose of pain medication, they may be reluctant to enroll. Rigorous chart review to increase number of screened participants and adequate education of clinical research coordinators will be necessary to enroll the appropriate number of participants.

Obtaining pain scores: As there are many points at which pain scores will be assessed during what is a fairly quick procedure, it may be difficult for both the clinical research coordinator to obtain and the participant to provide scores at the correct time points. Building a strong relationship with both the provider and the participant will be essential for obtaining the pain scores at the appropriate time points.

1.6 Expected outcomes of the study and dissemination of findings

If our hypothesis is true, our technique will be seen as non-inferior to a technique of cervical block using 20 mL 2-site injection to control cervical dilation pain. The implications of these findings give evidence for a new technique and could have large implications in terms of cost-savings, pain control, and side effect minimization.

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.

1.7 References

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