# SALUD: Self-Administered Lidocaine Gel for Pain Management with Uterine Devices: A blinded, randomized controlled trial

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# PROJECT SUMMARY

## 1. DESCRIPTION OF THE PROJECT

### 1.1 Rationale and objectives of the study

#### 1.1.1 Rationale

Despite global efforts to decrease discomfort during surgical abortion, pain remains a limiting factor in where and how abortions are performed. My primary fellowship research project focused on utilizing a self-administered lidocaine gel to decrease pain with first trimester surgical abortion, and found that there was no difference in pain level (as measured by VAS score) at time of cervical dilation between women randomized to the standard paracervical block group versus the lidocaine gel only group. Given that pain remains a limiting barrier for other gynecologic office procedures as well, we decided to apply this method of analgesia to intrauterine device (IUD) insertions.

For these procedures no standardized clinical guidelines for pain management exist. Reducing pain associated with IUD insertion may benefit patients and providers. When patients are comfortable during their procedure, it is likely the provider can more quickly and with fewer complications perform the insertion. It could also be argued these patients would report higher satisfaction with their procedure and provider [Kass-Wolf & Fisher, 2014]. To our knowledge, there is limited clinical consensus on pain management guidelines, demonstrating value in researching potential pain management solutions.

We propose to explore the effect of a locally applied vaginal lidocaine gel in place of the standard of care pain management (i.e. paracervical block or no intervention respectively) prior to IUD insertions.

SALUD (IUD insertion): We hypothesize that lidocaine gel is superior to placebo at decreasing procedural pain at a variety of time points throughout the procedure. This is a superiority, blinded, randomized controlled trial.

If self-administered vaginal gel is acceptable and effective, it would increase options for pain control during abortion and other gynecologic procedures (IUD insertion).

#### 1.1.2 Objectives and hypotheses

The objective of this study is to compare pain control at various time points during IUD insertions using a locally applied, patient-administered lidocaine gel as compared to standard of care (i.e. no pre-procedural analgesia).

If a patient-administered vaginal gel is acceptable and effective, it would increase options for pain control during these gynecologic procedures.

Hypothesis: Patients who receive 20 mL of 2% lidocaine gel self-administered 20-30 minutes prior to IUD procedures will have pain control superior to that of a placebo gel.

Primary Outcomes

- SALUD (IUD Insertion): Pain perceived by Visual Analogue Scale (0-100 mm) at the time of speculum removal

Secondary Outcomes

- Pain perceived at additional time points during/after the procedure:
    - Anticipated pain: measured upon clinic intake
    - Baseline pain: upon arrival to procedure room
    - After speculum placement
    - After tenaculum placement

Note: The research coordinator will stand at the head of the bed beside the patient with an iPad that has an enlarged VAS on it. They will ask the patient to tap somewhere along the VAS at these various time points to indicate their respective pain score.

**1.2 Previous similar studies**

While several previous studies have evaluated possible interventions for reducing IUD insertion pain, few have shown promising results. Although many providers recommend that patients take nonsteroidal anti-inflammatory drugs (NSAIDs) prior to the procedure, a 2009 Cochrane review concluded that NSAIDs are not effective at reducing pain during IUD insertion. The same review also concluded that the use of misoprostol to soften and open the cervix does not effectively reduce peri-insertional pain during insertion in nulliparous women, and may cause side effects. In a randomized trial, a 1% lidocaine paracervical block did not significantly decrease perceived pain with IUD insertion [Mody, 2012]. Randomized controlled trials by Allen et al. and McNicholas et al. examined the effect of 2% cervical lidocaine gel applied 3 minutes prior to the procedure. Both studies found no significant differences in pain scores with IUD insertion or tenaculum placement when compared with placebo.

To the best of our knowledge, there is no published data that 1) rigorously examines the effects of a prolonged time interval between local anesthetic administration and IUD insertion, or 2) explores whether adequate pain relief is possible through self-administered, non-invasive means alone.

In a soon to be published study conducted at Stanford (my primary fellowship project), self-administration of 20 ml of 2% lidocaine gel 20-30 minutes prior to first trimester surgical abortion was shown to be non-inferior to a traditional paracervical lidocaine block as a pain control approach. Given these promising results, we propose to

evaluate the effect of 2% lidocaine gel self-administered 20-30 minutes prior to IUD insertion in place of the standard of care pain management (i.e, no intervention).

## 1.3 Design and methodology

### 1.3.1 Research design and General Methodological Approach

This is a superiority, blinded, randomized controlled trial of women ages 18 and older undergoing elective IUD insertion. We chose a superiority approach based on the most commonly practiced method for pain management in these procedures (no intervention). In this study, participants and health care professionals will be blinded from the intervention/study group. Standard lubricating gel has the same clear gel appearance as lidocaine gel and will be used to ensure blinding. Due to logistical barriers with needing to prepare the gel immediately prior to insertion, the research coordinator responsible for enrolling and randomizing participants will not be blind to the intervention.

Participants will be recruited from Stanford Gynecology Clinic. Informed consent will be obtained prior to enrollment by a trained research coordinator after which, patients will be randomized to either group by block randomization. At the completion of the procedure, compensation will be given in the form of a $15 Target Gift Card or a $15 donation to a fund that assists low-income women obtain family planning services.

### 1.3.2 Criteria for the selection of subjects

**Inclusion Criteria:**
Women ages 18 and older presenting for elective IUD insertion (any type of IUD, copper or hormonal); at an out-patient setting at Stanford; English speaking, and ability to give informed consent.

**Exclusion Criteria:**

- Pre-operative use of misoprostol
- Allergy to study medications (lidocaine)
- Known uterine anomaly
- Prior cervical surgery
- IV conscious sedation

### 1.3.3 Subject Recruitment and Allocation

Potential participants will be identified for recruitment if scheduled for IUD insertion (regardless of type) at the Stanford University Gynecology Clinic. They will be approached by the research coordinator or study investigator and consented for the study. If enrolled, they will be randomized by block randomization. The research coordinator will prepare a 20ml pre-filled syringe with either 2% lidocaine gel or placebo, so that the physician/researcher is blinded to the group allocated. Participants will receive the treatment previously allocated on a rolling bases. The patient and provider will be blinded as to the treatment group.

All patients will then receive instruction on how to properly self-insert the study medication using a pictorial guide as previously employed in a similar RCT at this site (SALSA).

### 1.3.4 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. 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 Groups:

SALUD (IUD Insertion Arm):

No Intervention Group: As an alternative to lidocaine gel, participants will receive no intervention for pain management for IUD insertion (standard of care), but will receive placebo gel (standard lubricating gel).

### 1.3.6 Follow-up procedure

There is no extended follow-up planned for this study. Subjects will complete a survey at the completion of the procedure asking them to give a final pain score (secondary outcome) and assessment of overall acceptability (likelihood to recommend procedure or choose this form of pain control again). Any potential procedural complications will be managed using typical standard of care procedures for this clinic.

### 1.3.7 Criteria for discontinuation

Subjects will be able to withdraw from the study at any point during the procedure should they so choose.

### 1.3.8 Laboratory and other investigations

Not-applicable.

### 1.3.9 Data management

Data management will be done using RedCap, an electronic data capture program, and performed by the research coordinator and primary investigator (fellow).

### 1.3.10 Data analysis

SAS Version 9.3 and SPSS Version 23.0 will be used for data analysis.
Statistical Methods:

- Demographic characteristics will be examined among the randomized groups using Fisher's exact test
- Median VAS pain scores will be analyzed with Student's *t*-tests and non-parametric tests, respectively
- Linear regression may be completed in multivariate analysis to identify predictors of pain in an exploratory analysis

### 1.3.11 Number of subjects and statistical power

SALUD (IUD Insertion): The following power calculation accounts for continuous outcomes in a superiority trial

$$n = f(\alpha/2, \beta) \times 2 \times \sigma^2 / (\mu_1 - \mu_2)^2$$

- Effect size = 15% difference in VAS [Jensen 2003, Todd 1996, Rowbothom 2001]

- Mean outcome in control group: 36.7mm [Allen 2013]
- Standard deviation of VAS = 21.7mm [Allen 2013]
- Assuming $\alpha = 0.025$, $\beta = 0.10$, 90% power

SUMMARY: 200 patients are required to have a 90% chance of detecting, as significant at the 2.5% level, a decrease in the primary outcome measure from 36.7 in the control group to 21.7 in the experimental group. Accounting for drop-outs and protocol deviations by adding 10% to the number of participants, the total enrollment will be 220.

### 1.3.12 Study limitations

The potential limitations of this study include inability to blind the research coordinator given the need for preparation of the gel immediately prior to the patient's self-insertion, and the fact that this is a single site out-patient clinic at a university setting, that may not reach as widely as is desirable for the purposes of generalizability.

### 1.3.13 Duration of project

There are currently around 50 IUD insertions performed each month at the Stanford Gynecology Clinic, however we are tripling our IUD access clinics starting in July, so we anticipate over 100 IUD procedures per month. Estimating 30% enrollment, the anticipated length of the study is 7-10 months.

## 1.4 Project management

The study coordinator and investigator will be responsible for data entry in RedCap and export to SAS for statistical analysis and any required data cleaning. All data cleaning is tracked when done in this manner decreasing data entry, transposition and cleaning errors. The study coordinator will be responsible for maintaining locked files containing research study consents and any other paper documentation created. Remaining data collection will occur via the secure system, RedCap, using an iPad in the clinic with the patient and provider/study coordinator. Weekly research meetings are held at Stanford.

## 1.5 Links with other projects

Not-applicable.

## 1.6 Main problems anticipated

We do not anticipate any issues with enrollment or integration of the study into the Stanford Gynecology clinic and its daily operations. To ensure this, we have received approval from the clinic's manager to ensure fulltime assistance from a research coordinator.

## 1.7 Expected outcomes of the study and dissemination of findings

We hope to show that a self-inserted vaginal lidocaine is superior to the standard of care (no analgesia) with IUD insertion. If superior and acceptable to patient, a vaginal gel would offer an alternative route of pain control for an often uncomfortable procedure.

## 1.8 References


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## 2. ETHICAL CONSIDERATIONS

IRB approval has been sought and approval is pending from the Stanford University Research Compliance Office.

### 2.1 Informed decision & making and confidentiality

Please see the attached consent form (APPENDIX A). This form will also be translated into Spanish.

## 3. BUDGET

### 3.1 Line Item Budget / 3.2 Budget Justification

Please see the attached line item budget (APPENDIX B).

## 4. APPENDICES

- Appendix A: Sample Patient Consent Form
- Appendix B: Line Item Budget & Budget Justification