Transcutaneous Electrical Nerve Stimulation (TENS) for Pain Control During First Trimester Abortion: A Blinded Randomized Controlled Trial

Study Protocol and Statistical Analysis Plan

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Abstract
Surgical abortion remains the most common outpatient, gynecologic procedure in the world and most commonly occurs in the first-trimester(1). This procedure has been found, repeatedly, to be highly safe and efficacious(1, 2). Globally, women's access to abortion is largely determined by a number of extraneous circumstances. In the Untied States, among these determinants are political, geographical, social, and clinical factors. Clinical factors, including access to pain control, can contribute to access. A recent National Abortion Federation provider survey documented that 54% of respondents prefer the use of local anesthesia with IV sedation, deep sedation or general anesthesia(3). After receiving these types of sedation, women are unable to drive themselves—which can be problematic for many patients. Investing in modalities of pain control to expand the options available to women could lead to expanded access to abortion.

High-frequency, high-intensity transcutaneous electrical nerve-stimulation (TENS) is an inexpensive and non-invasive pain control approach. TENS, pulsating electrical currents that activate underlying nerves, does not have drug interactions or risk of overdose. Cochrane review of TENS for acute pain found inconclusive evidence(4). One previous abortion trial comparing TENS to IV sedation only looked at pain control in the recovery room(5). We propose a randomized controlled trial comparing TENS to IV sedation (in conjunction with local anesthesia) among women presenting for first-trimester surgical abortion. Primary outcome will be perceived pain by Visual Analogue Scale (VAS) during aspiration. Secondary outcomes will include other VAS scores and procedure time.

Specific aims
Through this single-blinded randomized controlled trial, we hope to demonstrate evidence that transcutaneous electrical nerve-stimulation (TENS) is an acceptable, non-invasive alternative pain control option for women undergoing abortion in the first-trimester. Ultimately, we hope to identify a pain control strategy that is inexpensive and does not carry anesthesia risk to expand access to abortion and make women more comfortable in low-resource settings, where access to pain control medications is limited.

Rationale
Worldwide, in 2010-2014, 25% of all pregnancies ended in abortion(1), making surgical abortion one of the most common gynecologic procedures. Globally, women's access to abortion is largely determined by a number of extraneous circumstances. In the Untied States, among these determinants are political, geographical, social, and clinical factors. Clinical factors, including access to pain control, can contribute to access. A recent National Abortion Federation provider survey documented that 54% of respondents prefer the use of local anesthesia with IV sedation, deep sedation or general anesthesia(3). After receiving these types of sedation, women are unable to drive themselves—which can be a problematic barrier to access for many patients. In the domestic and international setting, providing adequate pain control is a critical clinical quality measure. Investing in modalities of pain control to expand the options available to women could lead to expanded access to abortion.

Transcutaneous electrical nerve-stimulation (TENS) is a nonpharmacologic means of pain control that delivers electrical currents through the skin. These pulses of electrical current reduce pain by peripheral and central mechanisms, TENS actives descending inhibitory systems in the central nervous system to reduce sensitivity to pain (hypoalgesia). Assessment of previous TENS research identifies intensity as a critical factor in efficacy—documenting high intensity as the best means of pain control, as the higher pulse allows for deeper tissue afferents to be activated. TENS has been researched in a number of settings as pain control, including cancer pain, lower back pain, labor, and a range of gynecologic procedures and disorders. There is insufficient evidence to make broad conclusions regarding the efficacy of TENS in the majority of settings(6).

Previous research of abortion specific use of TENS, include the study of Platon et al. (2009), who assessed the use of TENS for the treatment of pain following surgical abortion. All patients received paracetamol, diclofenac, and fentanyl IV during general propofol anesthesia during the surgical abortion. The TENS intervention occurred in the recovery room, when patients reported their pain relief to be greater or equal to 3 on a visual analogue scale (VAS), where 10 was "worst pain imaginable". Patients were randomized to TENS or conventional pharmacological treatment (20-100μg fentanyl, mean dose 36.7μg, by IV). Platon et al. documented no differences between VAS scores before and after treatment (p=0.45 and p=0.09, respectively). More subjects reported a VAS of 0 ("complete pain relief") after the treatment in the TENS group (n=37, p=0.04). TENS subjects spent less time in the post-operative room(5).

This study has many limitations. While the authors demonstrated comparable pain control with TENS as compared to IV medication, the intervention was post-operative and all patients received deep sedation during their procedure. We hope to demonstrate TENS is an acceptable and comparable means of pain control for procedural pain during surgical abortion.

A recent study examined the use of TENS for pain relief during office hysteroscopy (rigid)(7). Lison et al. (2017) found TENS, compared to placebo, to be associated with a clinically significant reduction in VAS pain scores. Authors used high intensity TENS. While hysteroscopy is a very different procedure compared to first-trimester surgical abortion, we are motivated by the efficacy of TENS in the setting of hysteroscopy, as the time women experience the greatest pain with surgical abortion is when instruments enter the uterus.

TENS has not been previously studied as an alternative to intravenous (IV) pain control (traditionally, fentanyl and versed) in first-trimester abortion. We propose a single-blinded randomized controlled trial that compares TENS for pain control to IV conscious sedation. We hope to identify a means of pain control for first-trimester surgical abortion that is inexpensive, noninvasive, free of side effects, safe from complications, and easy to use.

Research design and methods

Design: Non-inferiority, single-blinded randomized controlled trial

Enrollment/procedure visit:

Women presenting to Planned Parenthood Mar Monte for first trimester surgical abortion (gestational age < 12 weeks) with IV sedation will be approached for enrollment. If the participant agrees to be blinded and randomized, she will be assigned a study ID. The patient will be 1:1 block randomized to one of two study groups following consent: 1) TENS or 2) IV sedation. Demographic data will be collected by research staff.

For participants randomized to the experimental group (TENS), care will be provided to the following protocol:

- A baseline and anticipated pain score will be collected using a Visual Analog Scale (VAS) pain assessment tool on a 0-100 mm scale (0 being no pain, 100 being worst pain imaginable) by research staff.
- The patient will have an IV placed by the center's nursing staff and will receive pre-procedure medications per clinic guidelines.
- Prior to the procedure, the patient will have two sets of two self-adhesive electrodes placed parallel to the spinal cord at the T-10-L1 and S2-S4 levels for TENS administration by research staff.
    - Non-blinded research staff will turn on the TENS unit 5 minutes prior to the procedure and monitor stimulating frequency level (see TENS administration protocol). The research staff will use a script with all patients to ensure patient blinding.
- Based on clinical guidelines, a physician will administer the IV medications (prepared prior to the procedure); participants in this arm will be administered saline solution for placebo.
    - A request for more pain control by the patient in this arm will be satisfied with an increase in TENS frequency.
    - Should the patient and/or provider identify the pain is not being managed and is unbearable; a protocol will be in place to ensure IV medications are readily available for administration as a rescue medication.

- The procedure will commence and various VAS pain scores will be collected at the completion of each of the following steps:
    - Speculum placement (time recorded)
    - Tenaculum placement
    - Paracervical block administration
    - Manual cervical dilation
    - Uterine evacuation
    - Speculum removal (time recorded)
- TENS unit will be turned off and electrodes removed.
- Overall VAS pain score will be collected.

For participants randomized to the control group (IV sedation), care will be provided to the following protocol:

- A baseline and anticipated pain score will be collected using a Visual Analog Scale (VAS) pain assessment tool on a 0-100 mm scale (0 being no pain, 100 being worst pain imaginable) by a research coordinator.
- The patient will have an IV placed and will receive pre-procedure medications per clinic guidelines.
- Prior to the procedure, the patient will have two sets of two self-adhesive electrodes placed parallel to the spinal cord at the T-10-L1 and S2-S4 levels.
    - Non-blinded research staff will turn on the TENS unit and connect the patient to the unit; however, the unit will not be delivering electrical stimulation. The research staff will use a script with all patients to ensure blinding between participants.
- Based on clinical guidelines, a physician will administer IV medication (prepared prior to the procedure); participants in this arm will be administered the standard dose of 100mcg fentanyl and 1mg midazolam.
    - Should the patient or provider request the patient receive more pain control, a “second dose” of pain medication, pre-prepared secondary dose vials will be made available. Maximum dose protocols of the clinical site will be followed.
- The procedure will commence and various VAS pain scores will be collected at the completion of each of the following steps:
    - Speculum placement (time recorded)
    - Tenaculum placement
    - Paracervical block administration
    - Manual cervical dilation
    - Uterine evacuation
    - Speculum removal (time recorded)
- TENS unit will be turned off and electrodes removed.
- Overall VAS pain score will be collected.

All groups:

- Post-procedure satisfaction questions will be administered to participants on a 0-100mm VAS (0 being “very dissatisfied” and 100 being “very satisfied”).
- Participants will rate their likelihood to recommend the pain control methodology to friends (0 being “very unlikely” and 100 being “very likely”).
- ISAS (Iowa Satisfaction with Anesthesia Scale) will be administered.
- Patients will be asked to ascertain which pain modality they were administered to evaluate effectiveness of participant blinding.
- Post-procedure provider questions will be administered.
    - Ease of procedure VAS score will be collected (0 being “very easy” and 100 being “very difficult”).
- Side effects and adverse events will be documented.
- Time spent in recovery before being discharged will be documented.

TENS Administration Protocol

The TENS unit to be used in this study is a TENS 7000 (ROSCOE Medical). TENS will be emitted asymmetric, biphasic square waveform at consistent pulse rate of 100 Hz and a width of 300 microseconds.

In the active TENS group, the TENS therapy will be initiated five minutes before starting the procedure and during the entirety of the procedure, until speculum removal.

Pre-Procedure Testing for TENS Group

1. Have the patient, with gown open to the back, sit upright on the exam table.
2. Place two self-adhesive electrodes parallel to the spinal cord at T10-L1 and S2-S4 levels.
3. Without having connected lead wire to electrodes or TENS unit, turn on the power of TENS 7000 unit, ensuring to not go above level 1 while adjusting settings.
4. Adjusting MODE

a. Push MODE button once until Normal setting has been selected.

5. Adjusting Width, Rate and Time

a. Push SET once to adjust Width. Use the up and down buttons until Width is set to 300 μs.
b. Push SET twice to adjust Rate. Use the up and down buttons until Rate is set to 100 Hz.
c. Push SET three times to adjust Time. Use the up and down buttons until the time is set to 60 minutes.

6. Maintaining the level of the TENS unit at level 1, connect the lead wire to the TENS unit and to the electrodes.
7. Ask patient if they are able to feel any tingling sensation while at level 1.
8. Instruct patient that you will be increasing the intensity until they are able to feel an uncomfortable, but not painful, tingling, pins and needles sensation. State that you will go slowly and that they should state when they begin to feel any kind of sensation. Reiterate that the sensation should not be painful.
9. Begin increasing intensity and record level at which patient begins to feel sensation and when it is at appropriate “slightly uncomfortable but not painful” stage.
10. Shut off unit, disconnect lead wires, and prepare for procedure.

No pre-procedure testing is necessary for IV Sedation Group. However, connect all electrodes to the IV Sedation Group, but do not connect the wires fully to the TENS unit.

The device’s intensity (amplitude) will be individually adjusted to each participant’s maximum sensory level (strongest reported tingling feeling without pain and with no muscle contractions). Patients will be counseled on the importance of maintaining the simulation at a maximum non-painful level. The TENS unit’s output intensity will be increased during the treatment every time the patient indicates they accommodated to the TENS stimulus.

Procedure TENS Administration for TENS Group

1. Once patient is prepared for procedure and IV solution administered, using settings listed above, increase intensity to the setting recorded from Step 9.
2. Ensure patient is comfortable with setting and instruct them that at any point during the procedure if they are feeling pain they can ask for you to increase the setting.
3. Signal to provider that you are ready for the procedure to begin.
4. Adjust setting as necessary throughout procedure, recording any adjustments you make in the Adjustment Log.
5. When the provider indicates that procedure is complete, notify the patient that you will be turning the TENS unit off. Turn off the unit, disconnect the lead wires, and remove the adhesive electrodes.

Procedure TENS Administration for IV Sedation Group

1. Once patient is prepared for procedure and IV solution administered, maintain blinding by telling the patient you are turning on the device (the device should not be fully connected to the TENS electrodes).
2. Ensure patient is comfortable and instruct them that at any point during the procedure if they are feeling pain they can ask for you to increase the setting.
3. Signal to provider that you are ready for the procedure to begin.
4. Adjust setting as necessary throughout procedure, recording any adjustments you make in the Adjustment Log.
5. When the provider indicates that procedure is complete, notify the patient that you will be turning the TENS unit off. Turn off the unit, disconnect the lead wires, and remove the adhesive electrodes.

For both groups, follow the rescue medication and second dose protocols.

Primary outcome:

- Procedural pain with aspiration as measured by VAS.

Secondary outcomes:

- Procedural pain at various time points:
  - Speculum placement
  - Tenaculum placement
  - Paracervical block administration
  - Manual cervical dilation
  - Speculum removal
- Procedure time

Exploratory outcomes:

- Provider perceived ease of procedure
- IV medication dose
  - Need for second dose
  - Need for rescue medication for TENS arm
- Participant satisfaction
- Complications
- Time spent in recovery
- Women's perceived group allocation

Criteria for the selection of subjects:

Inclusion criteria:

- Presenting for induced, surgical abortion
- Gestational age <12 weeks
- ≤ 18 years of age
- Agrees to be randomized

Exclusion criteria:

- Allergy to study medications (lidocaine, fentanyl, midazolam)
- ≥ 18 years of age
- Fetal demise
- Pre-procedure use of misoprostol
- No means of transportation following procedure
- Chronic substance use/abuse

Data Analysis:

Similar, previous studies have established that a difference of 30% or 13mm to 20mm difference on the 100mm pain visual analog scale (VAS) is considered clinically significant [Jensen 2003, Todd 1996, Rowbothom 2001]. Using the standard deviation from Conti et al. (2016) from VAS scores in the IV sedation and paracervical block group of SD±24.2, to detect at least a 15 mm mean difference on the 100 mm VAS with 90% power and a significance level of 0.05, a total of 90 participants are required for non-inferiority analysis. Adding 10% to compensate for potential participant drop out and protocol violation results in a total of 100 participants (50 per group). Randomized into block sizes of 4 and 6.

IRB APPROVED UPDATE on 5/29/2019:

To date, 7 participants have needed rescue medication in the TENS group and are not eligible for per protocol analysis. We will increase our overall n to 112 from 100. This will allow for a powered, per protocol analysis. Enrollment will cease when 45 participants in each arm have completed the study with complete per-protocol data for the primary outcome of pain of aspiration to satisfy the power calculation for this non-inferiority study. Non-inferiority studies need to be analyzed with per-protocol analysis.

Demographic characteristics will be compared between the two groups with descriptive statistics, specifically Chi-square test or Student's t-test where appropriate. Mean VAS scores will be compared to be consistent with published literature on VAS results. A t-test will be used to evaluate the primary outcome of pain at the time of aspiration. Median scores will also be assessed, as the data are not likely to be normally distributed; Wilcoxon's two-sample test will be used. To assess the mean change in pain score during the procedure and mean difference at various time points between groups, a mixed effects model and a repeated-measures ANOVA will be used. Univariate and multivariate analyses will be performed to evaluate potential confounders and determine independent predictors of pain at the time of aspiration.

Study data will be collected and managed using REDCap (Research Electronic Data Capture) tools hosted at Stanford University. Statistical analyses will be performed with SPSS Version 26 (IBM, Armonk, NY, USA).

Links with other projects
This project is not currently linked with any other projects.

Impact statement
The potential impact of the proposed research is far-reaching and applicable to abortion care in high- and low-resource settings. Reducing pain with surgical abortion mitigates a significant barrier to abortion care. In our current political climate in the United States, we may observe more women than ever traveling across state lines to access abortion care. Ensuring women who must drive or transport themselves (by bus or other travel means) have adequate pain control is important to ensuring quality abortion care. Internationally, women continue to receive abortion care in low-resource clinics and hospitals, many without the option to provide IV sedation—due to cost, provider level, or access to medical supplies. TENS is a low-cost strategy that many contribute to ensuring women access abortion under circumstances that are low-risk and comfortable.

Further, if TENS is found to be acceptable, IV sedation may be avoided—reducing a known complication risk associated with surgical abortion(8).

Results of this study will be submitted for presentation at professional conferences and peer-reviewed journals. Significant effort will be put into disseminating findings of this study.

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