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PROTOCOL TITLE: Transcutaneous electrical nerve stimulation (TENS) for pain control during cervical dilator placement prior to dilation and evacuation: A randomized controlled trial

PRINCIPAL INVESTIGATOR:

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VERSION NUMBER:

1

VERSION DATE:

12/4/18

STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	Primera TENS/NMES Unit with HAN Waveform by Chattanooga
IND / IDE / HDE #	
Indicate Special Population(s)	<input type="checkbox"/> Children <input type="checkbox"/> Children who are wards of the state <input type="checkbox"/> Adults Unable to Consent <input type="checkbox"/> Cognitively Impaired Adults <input type="checkbox"/> Neonates of Uncertain Viability <input checked="" type="checkbox"/> Pregnant Women <input type="checkbox"/> Prisoners (or other detained/paroled individuals) <input type="checkbox"/> Students/Employees
Sample Size	70
Funding Source	Society of Family Planning Research Fund
Indicate the type of consent to be obtained	<input checked="" type="checkbox"/> Written <input type="checkbox"/> Verbal/Waiver of Documentation of Informed Consent <input type="checkbox"/> Waiver of HIPAA Authorization <input type="checkbox"/> Waiver/Alteration of Consent Process
Site	<input type="checkbox"/> Lead Site (For A Multiple Site Research Study) <input type="checkbox"/> Data Coordinating Center (DCC)
Research Related Radiation Exposure	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
DSMB / DMC / IDMC	<input type="checkbox"/> Yes <input type="checkbox"/> No

STU#:

OBJECTIVES:

- Primary Outcome: Self-reported pain on 100mm VAS immediately following dilator placement
- Secondary Outcomes:
 - Self-reported pain at dilator exchange (if applicable)
 - Amount of time (in minutes) spent in clinic following dilator insertion
 - Self-reported highest level of pain between dilator placement and D&E
 - Number and type of adjunctive pain medications used
 - Patient acceptability

The hypothesis is that use of TENS will decrease pain by 20mm on VAS during initial dilator placement prior to dilation and evacuation, improving patient's overall pain management

BACKGROUND:

Dilation and Evacuation is the most common method of second trimester abortion. Studies have shown that adequate cervical preparation is necessary for the procedure to be performed safely and reduce the risk of complications. However, in the majority of cases the placement of these dilators is done with minimal pain management options. Previous research has shown that paracervical block reduces pain with laminaria insertion, (Soon et al., 2017) however despite this, the placement of dilators continues to be, for many, the most painful part of the dilation and evacuation procedure. Several studies have been performed comparing cervical dilation techniques and rated dilator placement pain as moderate to severe (Mercier & Liberty, 2014). Pain following insertion in the hours leading up to the dilation and evacuation has been rated as less severe, but persistent.

Transcutaneous electrical nerve stimulation (TENS) has been used in pain relief since 1965, when Melzack and Walls proposed using electrical stimulation as analgesia based on the gate control theory of pain relief (Johnson, Paley, Howe, & Sluka, 2015; Vance, Dailey, Rakel, & Sluka, 2014). TENS units are small, inexpensive, portable, battery-powered devices which deliver mild, alternating electrical currents via electrodes positioned on the skin near the anticipated dermatomal distribution of pain. The parameters of pulse frequency and pulse intensity are adjustable and linked to TENS efficacy (Vance et al., 2014). They overall have a favorable safety profile. Contraindications include electronic implants, such as cardiac pacemakers and implantable cardioverter defibrillators ("ELECTROPHYSICAL AGENTS - Contraindications And Precautions: An Evidence-Based Approach To Clinical Decision Making In Physical Therapy," 2010).

Two main theories have been proposed regarding how TENS provides analgesia. According to the "gate control" theory, neuromodulation may activate large myelinated afferent nerve fibers in the dorsal horn to inhibit transmission in primary afferent nociceptive fibers. The inhibitory input from the large myelinated afferent fibers is thought to be able to "close the gate" to prevent transmission of pain sensation. (Johnson et al., 2015). The endorphin-mediated theory of pain relief states that a stimulus outside the central nervous system can raise the level of endogenous endorphins and therefore provide analgesia. (Vance et al., 2014)

Despite usage of a paracervical block for pain control, patients still experience significant pain during dilator placement. If TENS provided pain relief for patients undergoing dilator placement prior to dilation and evacuation, this could provide an inexpensive, non-pharmacologic method of pain control that could be widely utilized.

STU#:

STUDY ENDPOINTS:

The study is a single-blinded randomized controlled trial to evaluate pain control using TENS during osmotic dilator placement prior to dilation and evacuation. The intervention group will use an active TENS unit and the control group will use a sham device. The primary objective is self-reported pain on 100mm VAS immediately following dilator placement. The secondary outcomes include self-reported pain at dilator exchange, self-reported highest level of pain between dilator insertion and dilation and evacuation, number and type of adjunctive pain medications used, and patient satisfaction with device. 70 patients will be included in a one to one allotment. The participants will have interaction with the study at two time points. The first is at the time of dilator placement and the second is at the time of dilation and evacuation the following day. No other interactions or long term follow up is needed.

STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S):

The device being used in this study is the Primera TENS/NMES Unit with HAN Waveform by Chattanooga. Chattanooga is a manufacturer of rehabilitation equipment for treating musculoskeletal, neurological and soft tissue disorders. It is a division of DJO Global. This device has been approved for pain control management and this is not a novel use for the device.

TENS units are small, inexpensive, portable, battery-powered devices which deliver mild, alternating electrical currents via electrodes positioned on the skin near the anticipated dermatomal distribution of pain.

The TENS units and electrodes will be kept in a locked cabinet in the Family Planning office on the 14th floor of Galter Pavilion, suite 200, which is the location of the research study and where the primary outcome will be measured.

PROCEDURES INVOLVED:

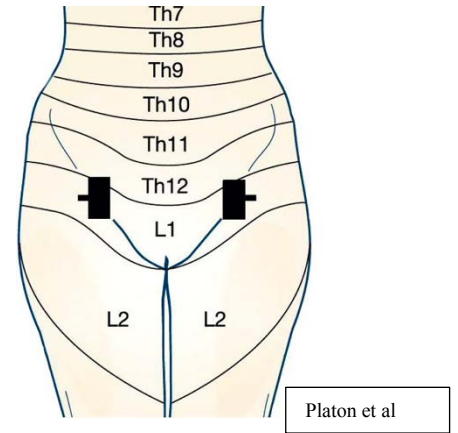
The proposed study is a single-blinded randomized controlled trial studying use of TENS for pain control during initial dilator insertion prior to dilation and evacuation. The participants will be randomized in a 1:1 randomization scheme using opaque, sequentially numbered envelopes following consent. The experimental group will have an active TENS unit – Chattanooga Primera – and the control group will have a sham TENS unit. The sham TENS will be the same unit without the true TENS electrical connections. The true TENS unit consists of the active unit and electrode pads connected to the unit via direct wires. The sham group will be given the active unit and have electrode pads placed but without wire connections. These participants will be told the device is a wireless device. They will also be told they may or may not feel sensation from the TENS. This will allow the device to be powered on and run in the same manner as the active group, but will not allow for electrical transmission between the unit and electrodes.

Based on power calculations, 56 participants are needed to detect a 20mm difference in VAS score with a standard deviation of 30mm. This is based on both minimum clinically significant difference in pain scores as well as previous studies regarding pain during dilator insertion. We will attempt to recruit 70 patients to account for possible TENS unit misuse or study dropout.

Eligible patients will be 18 years of age or older and between 14 weeks and 23 weeks 6 days gestation who meet inclusion/exclusion criteria as listed below. Two electrodes will be placed in

STU#:

the suprapubic area in the bilateral lower quadrants (as shown in the figure at right). The program that will be used is a high frequency (80Hz) program that runs for an hour in duration. It will be initiated 5 minutes prior to speculum placement. Participants will be instructed to increase the amplitude of the current as needed to provide analgesia but avoiding discomfort from the TENS stimulation. All participants will receive a paracervical block of 20mL 1% lidocaine with sodium bicarbonate followed by rigid dilation and dilator placement per standard cervical preparation protocol. Participants will complete 100mm VAS immediately following dilator placement. VAS is a 100mm line on sheet of paper with 0 being no pain and 100mm being worst pain of their life. The number of dilators, type of dilators, and use of adjunctive mifepristone/misoprostol will be according to providers' clinical judgement. Dilator placement will be performed by either Family Planning Fellow, PGY-3 OB/GYN resident, or Nurse Practitioner. All participants will receive prescriptions for twenty tablets of ibuprofen (600mg) and twelve tablets of hydrocodone/acetaminophen 5/325, which is the standard post-dilator insertion pain protocol for this clinic site. Participants will be allowed to leave prior to the end of the initial one-hour program. They will be sent home with instructions of how to run the TENS unit as needed for pain control.



Following the initial hour of use patients can re-activate the TENS unit as often as desired, using the same program. Participants will be given a log to record when TENS unit was used and whether additional pain medications were taken (attached). They will return their completed log and bring pill bottles on the day of surgery to confirm medications used.

Of note, in our practice a second set of cervical dilators is often placed 6 hours after first set in patients over 20 weeks gestation. During this placement the first set is removed, further rigid dilation is performed, and new dilators are placed per standard cervical preparation protocol. Pain score on 100mm VAS will be recorded following this dilator placement as well as a secondary outcome. Participants will run the TENS unit in the same manner as the initial dilator placement for dilator exchange.

On the day of surgery participants will record their highest interval pain score on 100mm VAS. They will also be asked their satisfaction with the TENS device. The TENS unit will be returned on the day of surgery.

The investigative procedures in this study are as follows:

- 100mm VAS immediately following dilator placement
- 100mm VAS immediately following dilator exchange (if applicable)
- 100mm VAS in the preoperative area rating highest pain level in the interval between dilator placement and surgery
- Log detailing when pain was felt in pre-operative interval period, TENS use or nonuse, and use or nonuse of adjunctive pain medication
- 5 Point Likert Scale determining patient satisfaction with TENS (attached)
- Demographic information sheet (attached)

VAS scoring and Log details will be completed on paper. Likert scale and demographics will be collected on tablets.

There are no plans for long-term follow up.

STU#:

DATA AND SPECIMEN BANKING

No data or specimens will be banked for future use.

SHARING RESULTS WITH PARTICIPANTS

Study results will be shared with the participants upon request. This request can be made at any point within the study time period.

Study results will be disseminated within the medical community via scientific publication in a peer-reviewed journal once study completion, data analysis, and manuscript approval has been achieved.

STUDY TIMELINES

The study will begin in March 2019 with participant recruitment. It is anticipated, based on a typical clinic volume of 400 patients requiring osmotic dilator placement prior to dilation and evacuation, that recruitment will take 12 months. Primary data analyses will then take place over the next two months, with plan to complete analyses by May 2019. Manuscript preparation, submission, and approval/publication will then occur.

An individual's participation in the study will be for no longer than 48 hours, which is the maximum amount of time between dilator placement and dilation and evacuation procedure. No further follow up will be required by the patient.

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria:

1. Women \geq 18 years of age
2. Gestational age between 14 weeks and 23 weeks 6 days
3. Willing and able to sign an informed consent in English
4. No contraindications to TENS

Exclusion criteria

1. Incarceration
2. Preterm Premature Rupture of Membranes or evidence of intra-amniotic infection
3. Presence of implanted cardiac device
4. Lack of sensation to touch on area of electrode placement
5. Prior TENS use
6. Opioid dependence

All patients between 14 weeks and 23 weeks 6 days gestation who schedule an appointment for a Dilation and Evacuation procedure with Northwestern Family Planning will be reviewed for study eligibility by the study team. All patients will be asked by clinical staff when scheduling an appointment if they have an implanted cardiac device or have used a TENS unit in the past. If eligibility criteria are met, then the patient will be approached regarding this study during the initial consultation appointment following description of dilator insertion procedure.

VULNERABLE POPULATIONS

The population being studied is pregnant women who have previously decided to have a termination of pregnancy or have an intrauterine fetal demise. They will confirm their decision for termination and consent to the termination procedure prior to being approached for study participation and subsequent TENS unit placement. TENS units have previously been studied

STU#:

during labor without adverse effects on the fetus. Therefore, the only potential risk would be patient discomfort from the TENS or allergic reaction to the electrode pads. These risks are rare and short-lived. Any fetal risk that has not previously been identified would be insignificant, as termination of pregnancy will occur 24-36 hours later.

PARTICIPANT POPULATION(S)

Accrual Number:	Category/Group: (Adults/Children Special/Vulnerable Populations)	Consented: Maximum Number to be Consented or Reviewed/Collected/Screened	Enrolled: Number to Complete the Study or Needed to Address the Research Question
Local	Pregnant Women	70	70
Study-wide			
Total:		70	70

RECRUITMENT METHODS

Study participants will be recruited at the Family Planning Clinic at Northwestern Memorial Hospital in Chicago, IL. This study will be registered with ClinicalTrials.gov per protocol. Participation will be completely voluntary. The Family Planning Clinic population is highly variable and includes patients with both Medicaid and private insurance. It includes patients referred from the greater Chicagoland area as well as from nearby states with more prohibitive abortion legislation. This clinic performs about 400 dilation and evacuation procedures requiring dilator placement per year.

Patients will be approached for informed consent by a study team member following determination of eligibility at the initial clinic termination consultation appointment at the Northwestern University Family Planning Clinic. No outsourced advertising for the study will be done.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

No compensation will be provided for the patients to participate in this study

WITHDRAWAL OF PARTICIPANTS

Participants may choose to discontinue participation at any time.

A participant would be discontinued from this study if they opted to discontinue the TENS unit prematurely during initial dilator placement or if an unexpected allergy to the electrode pads was noted during initial placement. Participants would be excluded from secondary analyses if they did not complete their pain log or agree to report pain/satisfaction with TENS on day of surgery, but would still be included in the primary analyses.

RISKS TO PARTICIPANTS

STU#:

Minimal risk to participants is anticipated with this study protocol.

The physical risk of this study is that the TENS may create a mildly uncomfortable sensation across the lower abdomen. The study participant will be instructed to increase the intensity of the TENS to provide analgesia without excessive discomfort from the unit, however, some discomfort may be felt for a short period of time as the participant is increasing and decreasing the intensity of the TENS. This discomfort is reversible, however, by decreasing the intensity or discontinuing use of the device. The participant may also have a contact allergic reaction to the electrode pads. This contact allergy is short lived and is easily treated with topical corticosteroids.

POTENTIAL BENEFITS TO PARTICIPANTS

If, as we anticipate, use of TENS improves pain control during dilator insertion, this would provide an inexpensive, non-pharmacologic method of analgesia with few contraindications. This could improve the patient experience during a necessary but extremely uncomfortable part of the abortion process.

DATA MANAGEMENT AND CONFIDENTIALITY

Data will be managed using REDCap. All data will either be entered directly into REDCap (with data collected on tablet) or will be entered manually by the primary investigator or research assistant. The paper forms and iPads will be stored in a locked cabinet in a locked office only accessible to the primary investigator and research assistant. All paper forms will be shredded in HIPAA bins following data entry.

Study participants will be compared on baseline characteristics using appropriate statistical methods depending on normal distribution (student t-test or chi-squared test) or non-normal distribution. Primary and secondary outcomes will be measured using appropriate statistical analyses for continuous or categorical data. A two-tailed p value of less than or equal to 0.05 will be considered statistically significant.

The number of subjects needed to show a 20mm reduction on VAS with a standard deviation of 30mm is 56, or 28 per arm. To account for subject discontinuation we will attempt to recruit 70 participants.

According to previous studies the minimum clinically significant difference in VAS is 15mm, however, this is within the standard deviation of typical VAS scores of pain during laminaria insertion and could confound study results. Soon et al previously used a 25mm reduction on VAS to calculate power in a previous study examining pain control during dilator insertion using paracervical block. We have chosen to use a 20mm reduction on VAS as this difference has shown significant in previous pain management research studies and we believe this to be a difference that will alter clinician practice patterns.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

This study does not involve more than minimal risk to the participants

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

On the day of their pre-operative abortion consultation appointment, a study team member will approach eligible patients regarding study enrollment. The questions they are asked regarding

STU#:

personal health information and demographics are questions that would be asked regardless of study participation.

The participants will enter their demographic information directly onto the iPad themselves or can have the research team enter it for them. They will be assured that their information will be protected as personal health information. Once enrolled, all participants will be given a study identification number. No PHI will be used to identify the participants moving forward within the study period.

COMPENSATION FOR RESEARCH-RELATED INJURY

N/A

ECONOMIC BURDEN TO PARTICIPANTS

No undue economic burden is anticipated for participants. Participants are not responsible for any costs for this research. Insurance will be billed for dilation and evacuation procedure per standard clinical practice.

CONSENT PROCESS

The consent process will take place in a private exam room following the abortion consultation prior to dilator placement. No waiting period will take place between informing the participant of the study and obtaining informed consent. The participant can discontinue involvement in the study at any time by notifying the study team. The individuals listed in the application will be directly responsible for the consent process. The minimum anticipated amount of time devoted to the consent process is 20-30 minutes. Participants will receive the same pain medication regimen whether they consent to the study and are in the control or study cohort or if they decline study participation. Eligible patients will be asked throughout the consent process if they understand the study and if they have any questions. They will also be asked to repeat in their own words what the study entails following the description of the study and consent discussion. Written consent will then be obtained.

WAIVER OR ALTERATION OF CONSENT PROCESS (consent will not be obtained, required information will not be disclosed, or the research involves deception)

N/A

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)

This research will use some medical record information (see attached demographics form). This information will be de-identified and attributed to a study ID number after consent is obtained. Patients will sign a HIPAA Authorization form at the time of consent.

NON-ENGLISH SPEAKING PARTICIPANTS

N/A

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

The Northwestern Family Planning Clinic performs about 400 dilation and evacuation procedures requiring laminaria placement per year. Therefore, we would need to recruit 17.5% of these patients for this study. This is a feasible percentage given that the alternative option for pain control is local anesthesia, which all patients receive regardless of study participation.

STU#:

Ashley Turner, MD is the primary clinical study team member of this study currently in her first year of the Family Planning Fellowship. She is in the clinic daily and will consent the majority of eligible patients. During the following year, she will be in her second year of the fellowship with few clinical responsibilities allowing for a large amount of time to be devoted to completing this study. Ashley Turner, MD has participated in multiple other research studies including studies looking at anesthesia and REM sleep in rats as well as immediate post-partum LARC outcomes and provider satisfaction.

The principal investigator is Leanne McCloskey, MD, MPH. Dr. McCloskey is an Assistant Professor of Obstetrics and Gynecology at Northwestern University and graduated from Northwestern's Family Planning Fellowship in 2015. She is currently director of the Ryan Program in Family Planning at Northwestern. She has served as both primary investigator and co-investigator on multiple research endeavors throughout her career. She has mentored both residents and fellows in the past during their research projects.

We do not anticipate patients requiring further medical or psychological resources secondary to this study. However, all patients presenting to the Family Planning Clinic who have decided on an abortion procedure are offered services of Perinatal Loss Social Work if needed. All persons involved in the study will be trained by Dr. McCloskey or Dr. Turner regarding study protocol and will be able to ask questions at anytime. We will also be available during the participant consent process to answer any additional questions. All personnel will be trained prior to study recruitment initiation.

STUDY-WIDE RECRUITMENT METHODS

N/A