PROTOCOL: Treatment of pain using a non-implanted intra-vaginal electrical stimulation device compared to sham device in chronic pelvic pain patients

BACKGROUND

Chronic pelvic pain (CPP) is a complex and devastating diagnosis, encompassing multiple different conditions. Many organ systems may be involved including musculoskeletal, neurologic, genitourinary, psychiatric or gastrointestinal systems. Furthermore, it can be associated with major insomnia, psychosexual trauma, and mood disorders resulting in challenging cases characterized by pain that is refractory to standard treatment modalities. In a study conducted by Mathias et al., one in seven women experience chronic pelvic pain. The economic burden can be substantial, with previous estimates of 2.8 billion dollars per year (1).

Dyspareunia is defined as recurrent or persistent pain associated with sexual intercourse and affects approximately 8-21% of women in the United States (19, 20). Understandably, women with dyspareunia often suffer a decline in sexual functioning. It may lead to decreased arousal, loss of libido, and anorgasmia. However, its impact extends beyond sexual functioning as it can affect a woman's reproductive health and overall sense of well-being. Previous estimates indicate that 88% of sexually active chronic pelvic pain patients report pain during or after intercourse (1).

Treatment of chronic pelvic is challenging due to a poor understanding of pain processing and physiology. Each patient's experience of pain is unique and may be any combination of visceral, neuropathic, or even somatic in etiology. Persistent pain despite aggressive treatment of organic etiologies may imply a psychogenic overlay. A comprehensive and integrative approach is ideal and may include physical therapy, medications, or cognitive behavioral therapy.

Pelvic floor physical therapy is an effective treatment. Pelvic floor rehabilitation addresses the pelvic floor dysfunction and may include manual therapy, transvaginal biofeedback and electrical stimulation. Reissing et al. performed a retrospective chart review and discovered that physical therapy, particularly internal manual techniques, is a successful technique in treating patients with vaginismus (5). Electrical stimulation (ES) to the pelvic floor is an effective treatment in vaginismus, vulvar vestibulitis, urinary urgency, and levator ani hypertonus (11-15). ES delivered specifically through a transcutaneous electrical nerve stimulator (TENS) unit results in notable benefit in pain and dyspareunia (8,12, 21-23). Murina et al. conducted a randomized controlled trial comparing use of a vaginal probe delivering electrical stimulation to a sham device. In this study, they used a TENS unit to treat vestibulodynia using a protocol of 15 min of 10 Hz followed by 15 minutes of 50 Hz. These sessions were completed on a twice per week basis for 10 weeks. Pain scores, dyspareunia and overall sexual functioning were significantly improved in the active arm compared to placebo (8). Another study used a TENS unit to treat primary dysmenorrhea. In this protocol, the TENS unit was set to 100 Hz with 100ms pulse width for the first 8 hours of the menstrual cycle and then repeated for another menstrual cycle (9). A smaller study of 12 women used electrical stimulation biofeedback and gradual desensitization in the treatment of vaginismus. After treatment, all 12 women were able to have vaginal intercourse (13).

Electrical stimulation is used extensively for the treatment of various pain disorders. It is delivered through peripheral nerve stimulation, a TENS unit, or sacral neuromodulation using an implantable device. Electrical stimulation has three different programmable settings including the frequency, intensity and pulse duration. High frequency is considered as > 50 Hz whereas low frequency is < 10 Hz. The intensity, also known as the power, of the unit can be set to a sensory or motor threshold with any frequency (2).

There are several theories to explain the mechanism of action of electrical stimulation. TENS works by altering the ability to perceive pain signals. The gate theory is one proposed mechanism of action. Electrical stimulation of nerves via a specific dermatome results in a blocking or gating effect at

the dorsal horn of the spinal cord. This inhibits the transmission of pain impulses to the upper nervous system. Also, low frequency stimulation of the dermatome can increase the level of endorphins, providing pain relief. (2) The sacral nerve roots 2-4 hold the autonomic and somatic innervation of the pelvic floor, bladder, and urethra. Therefore, stimulation of the sacral nerve roots 2-4 can provide a means to modulate impulses from the pelvic floor. Inhibition of afferent innervation from the pelvic floor or bladder is achieved with afferent activation of the sacral nerve roots using Interstim® or similar devices. In other words, stimulating the sacral nerve roots through neuromodulation has an inhibitory effect on pain pathways at the spinal cord level. (3)

Treatment of chronic pelvic pain may include peripheral nerve stimulation via the posterior tibial nerve. This mixed nerve shares the same spinal origin as the innervation of the bladder and pelvic floor. Stimulation of the posterior tibial nerve travels retrograde to modulate the afferent input from the bladder or pelvic floor. (4) Therefore, it shares a similar mechanism of action to sacral neuromodulation but spares the patient the complications associated with surgical implantation of a device.

Despite its efficacy and benefits, electrical stimulation is time intensive and dependent upon a health care provider's schedule. It often causes the patient social embarrassment resulting in its inaccessibility. Although electrical stimulation provides pain relief, even highly motivated patients report that anxiety prohibits them from participation in physiotherapy (6). We propose a novel treatment using a non-implanted intra-vaginal electrical stimulation device to be used in the comfort and privacy of the patient's home. This addresses several barriers associated with in office, standard pelvic floor physical therapy. Furthermore, a personal device allows the patient a more active role in her treatment, which can be empowering and ultimately, therapeutic.

InControl Medical created a line of products FDA approved for urinary incontinence and fecal incontinence (10). These devices are non-implanted, customizable, battery-operated vaginal probes made of medical grade silicon and provide electrical stimulation to the pelvic floor. One of the devices, ApexM™ provides electrical stimulation at frequencies alternating between 13 Hz and 50 Hz and allows the clinician to adjust the intensity as well as the duration of the electrical stimulation. We propose the use of low power electrical stimulation for the treatment of pain in patients diagnosed with CPP. We will deliver the electrical stimulation using ApexM™, adjusting the power to a sensory threshold to prevent muscle contraction.

Primary goal:
To evaluate the use of a domiciliary intravaginal, non- implanted electrical stimulation device in the treatment of chronic pelvic pain. Hypothesis: ES will decrease pain as measured by the visual analog scale and brief pain inventory (18).

Secondary goals:
To evaluate the effect of ES on overall quality of life. Hypothesis: ES will improve quality of life as measured by the Short Form-36. (16)
To evaluate the effect of ES on sexual function. Hypothesis: ES will improve sexual functioning as measured by Female Sexual Function Index (17)
To evaluate the use of ES on use of pain medications. Hypothesis: ES will decrease dosage and frequency of pain medication use. This will be measured by use of a daily pain medication journal. Patients will complete a journal listing the type, amount and dosage of pain medications used on a daily basis.

SIGNIFICANCE
If a positive effect is seen, a personal vaginal device designed for home use can be offered to patients with chronic pelvic pain. Patients would be able to take pelvic floor rehabilitation from the physical therapy office into their home. Furthermore, it would justify a larger, multi-center, randomized

controlled trial comparing the ApexM™ device to standard in office physical therapy.

STUDY DESIGN

Our study is a prospective, randomized controlled trial in patients diagnosed with chronic pelvic pain. To make the diagnosis, patients must have non-cyclic pelvic pain for duration greater than 6 months which results in functional disability. This is defined as patient reported limitations in social or occupational functioning. One physician will make the diagnosis from patients evaluated in one treatment facility. Inclusion criteria: women >/= 18 years old who are sexually active or desire to be sexually active, no active infection, diagnosed with non-cyclic chronic pelvic pain, duration of symptoms greater than 6 months, neurologically intact, able to accommodate and tolerate the device, not pregnant and not attempting to achieve pregnancy. Exclusion criteria include pregnancy, currently active in pelvic floor physical therapy, active malignancy, patients unable to contract their pelvic floor secondary to causes such as myelopathy, spinal cord trauma, patients with diabetes, vestibulodynia, vulvodynia, a pacemaker, defibrillator or other implanted neuro-modulatory devices, patients with a hypotonic pelvic floor, or those currently on treatment for pain with topical lidocaine, gabapentin or other medications or injections outside of standard analgesics, and severe psychiatric disorders. We will instruct patients to avoid starting any new medications for the treatment of their pelvic pain during the trial.

We will invite subjects meeting criteria to participate in the study. If subjects are interested, they will review and sign the informed consent. Randomization is based on age, diagnosis, and duration of symptoms. Researchers will collect the patient's demographics and general medical history at the initial visit. This includes relevant past medical history, surgical history, allergies, medicines, and social history. At each visit, we will assess pain, quality of life and sexual function. Pain is assessed using the visual analog scale, quality of life measured by the SF-36, sexual dysfunction measured by the female sexual function and pain medication use by a daily journal. We ask each subject to record the date, each completed session, as well as pain medication usage in a provided daily journal. We will make these assessments at baseline, 4 weeks, 8 weeks and 12 weeks.

The patients randomized to the treatment arm will be trained and fitted for the device at their initial visit. The researcher will instruct on how to properly apply the conductive gel, insert the device to a minimum depth of 4 inches, and inflate until comfortably snug. The intensity is set exclusively by the physician to a tolerated sensory level. We will not elicit a muscle contraction. At the target amplitude, patients will feel a non-painful fluttering or tapping sensation, but will not have pelvic floor muscle contraction. We ask each subject to complete her first session at the office. She will lay quietly, supine with knees flexed for 12 minutes with the device powered on and set to the previously determined stimulation level. Subjects will perform this for 6 sessions per week at 12 minutes per session for an additional 12 weeks. Both treatment arms will have a sound clip of peaceful music lasting 12 minutes which signals the end of a session. At each follow-up visit, we will re-evaluate the stimulation level and adjust to avoid muscle contraction.

Subjects in the control arm will use a sham ApexM device. The original ApexM device will be modified to disable its electrical stimulation functionality. Otherwise, the devices are indistinguishable and possess identical dimensions and customizable probe. At the initial visit, we will fit the subjects and directly observe their first 12 minute session. After placing the device intra-vaginally, we will instruct them to lie quietly in a supine position with knees flexed for 12 minutes. Subjects in this arm will complete the same protocol of 12 minutes per session, 6 times each week for 12 weeks.

The ApexM device has a built-in feature to measure compliance. Using the device keypad, the clinician can activate the compliance tracker which utilizes a series of lights. Each illuminated light accounts for the completion of six ApexM sessions. The clinician can also reset and clear the compliance tracker. At each follow-up visit, after documenting the number of illuminated lights, we will reset the compliance tracker in order to record compliance for the following four weeks. Only the clinician will have the code to activate and reset the compliance tracker. If the subjects are compliant, four illuminated lights should appear at each follow-up visit. Both the original and sham device is equipped with the compliance feature. Additionally, subjects will complete a daily journal documenting each session over the course of 12 weeks. Chronic pelvic pain patients suffer from persistent and refractory pain and generally are very motivated to comply with therapy. Barriers to compliance with standard in-office pelvic floor physical therapy are addressed by offering a personal device utilized at home.

During the study, we ask that all subjects refrain from starting other treatment modalities except standard analgesics including acetaminophen or NSAIDs for the 12 weeks. This includes hormonal therapies, new oral or topical medications, pelvic floor physical therapy, and psychotherapy.

DATA ANALYSIS

We will record demographics, general medical information, questionnaires, and medication usage (including frequency and doses) using the REDCap database designed by the researcher and hosted by the Cleveland Clinic. REDCap (Research Electronic Data Capture) is a secure, web- based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. The database will be reviewed by a statistician prior to data collection. Only the PI and research co-investigators will have access to the stored information. Only the PI, co-PI's and those responsible for analysis will have rights to export identifiable data. The subject's personal health information will be stored in the secure research database and only limited research personnel have access to this database. Great care will be taken to ensure that confidential health information is stored securely and accessible only to the PI and co-investigators.

RANDOMIZATION

In order to minimize bias in the study, we will stratify subjects based on presence or absence of levator spasm.

STATISTICAL METHODS

Numerical values will summarized by mean and standard deviation when they appear to have a normal distribution; otherwise, they will be summarized by median and interquartile range. Categorical values will be summarized by frequency and percentage. Univariable comparisons between groups will be made using two sample t-tests, Wilcoxon rank sum tests, or Chi-square tests, depending on the level of measurement and data distributions.

STUDY AIM ANALYSIS

1. Change in pain score from baseline to 12 weeks will be compared using a two-sample t-test. A multivariable linear regression model may be considered if baseline differences between groups are observed.
2. Changes in SF-36 subscores from baseline to 12 weeks will be compared using Wilcoxon rank sum tests.
3. Changes in FSFI subscales from baseline to 12 weeks will be compared using Wilcoxon rank

sum tests.

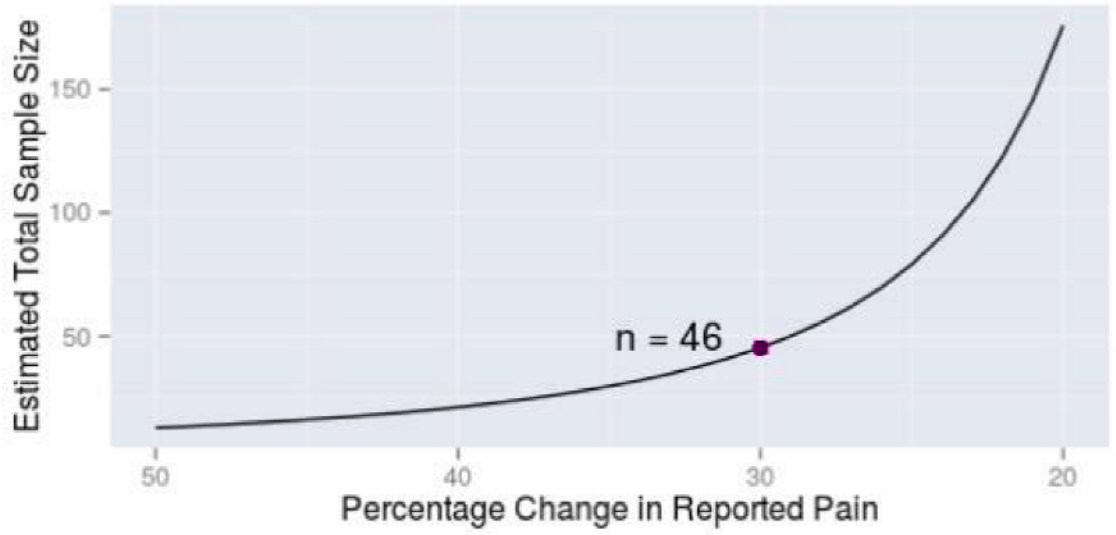
4. Frequency of medication from baseline to 12 weeks may be compared using a poison regression model. Dose of medication will be compared using a Wilcoxon's rank sum test.

Additional analyses using longitudinal methods, including linear mixed effects models and generalized linear mixed effects models, may be used in subsequent analyses to explore the length of time that elapses before the treatment benefit is observed. In all analyses, statistical significance will be determined by a p-value less than or equal to 0.05. Analyses will be performed using R version 3.1.1 (2014-07-10) statistical software (or a later version).

Two interim analyses are planned for this study, to be conducted at 25% recruitment and 50% recruitment. These analyses will be conducted using significance levels of 0.017 and 0.033, respectively. A stopping rule will be applied of any statistically significant increase in pain from baseline as reported on the visual analog scale. The percentage of patients dropping out from the study will also be monitored, with a significantly higher percentage of electrical stimulation patients dropping out being considered a potential safety issue.

POWER ANALYSIS

The researcher currently estimates typical reported pain from this population of patients to be between 8 and 9 on a 10 point scale. A clinically meaningful improvement would be a 30% reduction in reported pain. For the purposes of the power analysis, we assume that the placebo effect of the sham treatment may reduce reported pain by 10%. We assign the mean baseline pain value of 8.5 to each group with a standard deviation of 1. A 30% reduction in pain corresponds to a mean score of 5.9 and a 10% reduction of pain corresponds to a mean score of 7.7. The sample size analysis is based on a two-sample, two-sided t-test with a significance level of 0.05 and 80% power. The sample size analysis indicates that for a 30% reduction in pain, a total sample size of 46 is required to provide 80% power for the study. To reduce the impact of attrition on the final study results, we plan on recruiting 10% more than the minimum sample size. This amounts to a total of 52 patients (26 patients per arm).



ADVERSE EVENTS AND DATA SAFETY MONITOR

Patients are asked to record any side effects, adverse effects and unanticipated problems daily. In

addition to documenting these in a daily journal, we will encourage them to call and report these events. Each follow-up visit will evaluate and address any adverse event. The principal and co-investigators will review all adverse events and immediately report new events to the IRB. Our study will use a data safety monitor for adverse events. This individual has clinical expertise with chronic pelvic pain and will be blinded to the treatment arms. Monitoring will include assessments at 25% and 50% subject enrollment. If the data indicates harm, as described above in study aim analysis, the trial will be prematurely discontinued.

CONSENT

The principle investigator and co-investigators will consent the subjects in a private examination room. We will give all information in a clear and understandable manner and address all questions to the subject's satisfaction. Further emphasis will be made on the optional nature of this study and future care of the subject will not be dependent on participation.
Subjects who meet inclusion and exclusion criteria will be invited to participate at which time the study purpose, procedures, and requirements will be communicated. If she is interested in participating, she will sign the consent form and return for the initial study visit. Randomization will be performed at that subsequent visit. If the patient is unsure, she may leave and sign the consent form at the subsequent visit if still interested.

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