Transcutaneous Electric Nerve Stimulation For Pain Control During Office Intra-detrusor Onabotulinumtoxin A Cystoscopy Injection for Overactive Bladder: A Phase III Randomized Controlled Trial

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TRANSCUTANEOUS ELECTRIC NERVE STIMULATION FOR PAIN CONTROL DURING OFFICE INTRA-DETRUSOR ONABOTULINUMTOXIN A CYSTOSCOPIC INJECTION FOR OVERACTIVE BLADDER: A PHASE III RANDOMIZED CONTROLLED TRIAL

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Study Summary

Title	Transcutaneous Electric Nerve Stimulation For Pain control During Office Intra-detrusor Onabotulinumtoxin A Cystoscopy Injection for Overactive Bladder: A Phase III Randomized Controlled Trial
Running Title	TENS Units for Pain Control During Office Cystoscopic Botox Injections
Protocol Number	20-003510
Phase	Phase III
Methodology	Two Arm Phase III Double Blinded Randomized Placebo Controlled Trial
Overall Study Duration	12 months
Subject Participation Duration	2 days
Single or Multi-Site	Single Site
Objectives	Primary Objective(s): To determine the effect of Transcutaneous Electric Nerve Stimulation (TENS) units on pain experienced by women undergoing office cystoscopic intradetrusor onabotulinumtoxin A injection for overactive bladder
Number of Participants	60
Diagnosis and Main Inclusion Criteria	1. Age ≥ 18 2. Scheduled to receive Intradetrusor Onabotulinumtoxin A injection for Overactive Bladder 3. English speaking
Study Product, Dose, Route, Regimen	Product: TENS Unit Dose: Asymmetric, balanced, biphasic square waveform at a mixed stimulating frequency that randomly varying between 80 and 100 Hz and a pulse duration of 300 microseconds Route: Transcutaneous using Adhesive Pads

Duration of Administration	To start 5 minutes before the procedure and during the procedure
Reference therapy	Current Standard of Care: Intra-urethral Lidocaine, Intra-vesicle Lidocaine Solution, Distraction techniques, Aromatherapy
Statistical Methodology	The data will be analyzed using an intention-to-treat approach. In order to account for individual participant pain sensitivity profiles through the experiment, random effect longitudinal model will be adjusted to the data controlling by treatment and selected covariates at baseline.

1 Introduction:

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 *Background*

Options for adequate pain control during office-based cystoscopy procedures are limited [1]. Currently, varying pain control strategies are being used including local anesthesia (intra-urethral lidocaine [2], intra-vesicular lidocaine solution[1, 3]), distraction techniques[2, 4] (conversation/music/'squeeze balls'), aromatherapy[5], intramuscular analgesia, sedation and a combination of these techniques. Despite this, participants often experience pain during the procedure. Trans-cutaneous Electrical Nerve Stimulation (TENS) is a non-pharmacologic, non-invasive and safe method of pain control that involves delivery of electrical impulses to the skin, resulting in a reduction in perceived pain. TENS units have been successfully used for intraoperative pain control during office hysteroscopy[6] and office colonoscopy[7]. They may also help reduce pain during cystoscopy. Overactive bladder (OAB) is a symptom complex pronounced by urinary urgency, affecting up to 12% of the adult population, with a significant negative impact quality on the life [8]. Cystoscopic Intradetrusor Onabotulinumtoxin A is used for the treatment of OAB in participants who do not tolerate or adequately respond to oral anticholinergic medications[9]. The response to the onabotulinumtoxin A injection is transient and requires repeat injections roughly every 6-7 months. Adequate pain control during this procedure is essential for success in the office setting [10, 11]. There is a critical need to assess the effectiveness of TENS units for intraoperative pain management during office cystoscopic Intradetrusor Onabotulinumtoxin A. In the absence of such knowledge, the realization of the pain control potential of TENS units during office cystoscopy will remain unknown.

1.2 *Overactive Bladder and Cystoscopic Intradetrusor Onabotulinumtoxin A*

Overactive bladder (OAB) is a symptom complex that includes urinary urgency, frequency, urgency incontinence, and nocturia. It is highly prevalent, affecting up to 12% of the adult population, and can significantly impact quality of life (8). In 2013, FDA approved Intradetrusor Onabotulinumtoxin A for the treatment of overactive bladder symptoms in patients who do not tolerate or adequately respond to oral anticholinergic medications(9). Of note more than 50% patients starting medical therapy discontinue medical therapy by 6 months(13). The therapy is performed by a cystoscopic injection that can be carried out in an office setting with topical analgesia or under sedation in the operating room. The response to the onabotulinumtoxin A injection is transient, requiring repeat injections roughly every 6-7 months (10, 11). Due to the need for repeat injections, performing this procedure in the office is cost effective (14). Adequate pain control during this procedure is essential for success in the office setting. A limited number of studies have looked at measures to improve pain control with office cystoscopic onabotulinumtoxin A injections. LeClaire et al. (2018), in a randomized control trial of 26 participants undergoing office cystoscopic onabotulinumtoxin A injection for overactive bladder randomized to a belladonna and opiate suppository group (n =13) and a placebo suppository group (n = 13), found that the belladonna and opiate did not significantly reduce bladder injection pain(1). Nambiar et al. (2016) in a randomized control trial of 54 participants undergoing office cystoscopic onabotulinumtoxin A injection for overactive bladder randomized to receive intravesical alkalinized lidocaine solution group (n =26) and intravesicle lidocaine gel (n = 28), found that alkalinized solution was not superior to lidocaine gel(3).

1.3 *Adequate Pain Control During Office Cystoscopy*

Operative office cystoscopy is a painful procedure and often results in preprocedural anxiety in patients (1-4). Flexible cystoscopy maybe less painful than rigid cystoscopy (4). Options for adequate pain control during office-based cystoscopy procedures are limited (1). Currently, varying pain control strategies are being used including local anesthesia (intra-urethral lidocaine (2), intra-vesicular lidocaine solution (1, 3), distraction techniques (2, 4) (conversation/music/'squeeze balls'), aromatherapy(5), intramuscular analgesia, sedation and a combination of these techniques. Despite these interventions, patients often experience mild to moderate amount of pain during the operative office cystoscopy (1, 3).

1.4 *Trans-cutaneous Electrical Nerve Stimulation (TENS) in an Office Setting*

Trans-cutaneous Electrical Nerve Stimulation (TENS) may provide satisfactory pain control in the office setting. It is easy to access and use following proper training. There is a lack of side effects compared to existing pharmacology pain control methods and the lack of need for in-office anesthesia personnel and prolonged post-procedural monitoring. There are limited studies looking

at TENS unit for intraoperative pain management. In order to get the best analgesic effect from the TENS unit, it is now known that accurately placement of electrodes, and selection of the appropriate current waveform, waveform duration, frequency and intensity are essential [6, 12]. With regards to electrode placement, it is important place the electrodes near the nerves that supply the area where the analgesic effect is needed [6, 13]. Hruby et al (2016) in a randomized control trial of 148 patients in 2006 undergoing flexible cystoscopy showed no difference in mean visual analogue pain score between the no analgesia group, placebo TENS group and activated TENS (mean visual analogue pain score of 3.73, 3.65, 3.52 respectively, p= 0.97). In this study, the electrodes where placed halfway along an imaginary line between the anterior superior iliac spine and the pubis. Such a placement has been shown to be suboptimal in achieving pain control for pelvic procedures. Also, in this study the pulse duration was set at 180 microsecond pulse width. The current consensus is the pulse duration of greater than 250 microseconds is important to achieve adequate analgesia [6, 13]. Studies have shown a reduction in pain with the appropriate use of TENS units during office hysteroscopy[6] and during colonoscopy[7].

1.5 *Innovation*

The long term goal is to contribute towards effective pain control strategies for office based operative procedures. Our overall objective in this application is to determine how TENS units affect pain control during office cystoscopic Intradetrusor Onabotulinumtoxin A injections. This is will be the first study looking at the effectiveness of TENS units for pain control during office cystoscopic Intradetrusor Onabotulinumtoxin A injections. It was also be the first study looking at the effectiveness of TENS units for pain control during office cystoscopy in general, using appropriate TENS settings. The knowledge gained from this study will have widespread implications for pain control during office based cystoscopic procedures in the field of Urogynecology and Urology, and can be extrapolated to other office based procedures in other fields as well. If TENS units prove to be effective in pain control for office based procedures, this will lead to a paradigm shift.

1.6 *Choosing the Specific Aims of this Study:*

Prior to 2017, we performed all cystoscopic Onabotulinum Toxin A injections in the operating room at Mayo Clinic in Rochester, Minnesota. Patients with refractory overactive bladder require repeat injections and had to return to the operating room on average every 6-7 months. This would be almost a whole day's ordeal for patients. In order to minimize the inconvenience to patients and to provide cost effective patient care, Cystoscopic Onabotulinum A injections were transitioned to the office setting in 2017.

For successful adoption of office cystoscopic Onabotulinum Toxin A injection, the procedure has to be an acceptable option to patients. As noted earlier, office cystoscopy in itself is an uncomfortable procedure and the addition bladder injections make it painful. The pain patients experience during the procedure can deter them from wanting a repeat cystoscopic injection in office setting. Currently we use local anesthesia (intra-urethral lidocaine), intra-vesicular lidocaine solution, distraction techniques (conversation/music/'squeeze balls'), and aromatherapy for pain control during this procedure. Despite this, a preliminary review of 91 office Cystoscopic Onabotulinum A injections performed at our institution from 2017 to 2019 showed that the average intra-procedural pain score was 5 on a numerical pain scale of 0 to 10.

Therefore, we chose the pain experienced during the office Cystoscopic Onabotulinum Toxin A injection and the patient's satisfaction from the procedure as the specific aims for this study.

2 Study Objective(s)/Aims(s):

2.1 *Specific Aim #1: To assess whether the TENS units are effective for intraoperative pain management during office cystoscopic Intradetrusor Onabotulinumtoxin A in women with OAB.*

We plan to compare participant reported pain using a 0-10 numerical pain scale at baseline, during and after cystoscopic intradetrusor onabotulinumtoxin A injection in patients randomized to active TENS units and placebo TENS units. We will compare the change in numerical pain scale from baseline to intraoperatively and intraoperatively to postoperatively between both groups.

2.2 *Specific Aim #2: To evaluate the effect of TENS units on participant satisfaction following cystoscopic intradetrusor onabotulinumtoxin A injection in women with OAB.*

We plan to evaluate participant satisfaction on a 10 point Likert scale immediately after the procedure in participants randomized to activated TENS units and placebo TENS units.

3 Study Design

3.1 *General Description*

The study is a two arm phase III double blinded randomized placebo control trial looking at the effect of TENS unit on pain in participants receiving Office based Cystoscopic Onabotulinum Toxin A injection for Overactive bladder at the Mayo Clinic in Rochester, Minnesota.

3.2 ***Number of Subjects:*** 60 subjects

3.3 ***Duration of Participation:*** From accrual to the end of the Cystoscopic Onabotulinum Toxin A injection office visit

3.4 ***Study Schema and Flow:***

3.5 *Primary endpoints*

- Numeric Analog Pain Score (0-10) at Baseline before Office Cystoscopic Onabotulinum Toxin A injection (collected after the participant changes into procedural grown)
- Numeric Analog Pain Score (0-10) during Office Cystoscopic Onabotulinum Toxin A injection (collected during middle of the procedure, after the 10th injection)
- Numeric Analog Pain Score (0-10) after Office Cystoscopic Onabotulinum Toxin A injection (collected 5-10 minutes after the procedure)

Source: The Numerical Analog Pain Score will be documented by the study coordinator into the case report forms and later transferred in the Red Caps Data Management system.

3.6 *Secondary Endpoints*

- Participant satisfaction on a Likert Scale of 1 - 10 (10 = Completely satisfied and 1 = Completely Dissatisfied*)* after the Office Cystoscopic Onabotulinum Toxin A injection (collected 5-10 minutes after the procedure)
- Depression Screen Score (PHQ 9)
- Anxiety Screen Score (GAD 7)
- History of Sexual Abuse
- History of Chronic Pelvic Pain
- Participant Demographics: Age, Ethnicity, Basal Metabolic Index (BMI), Insurance
- Co-morbid conditions
- Current Medications
- Smoking Status
- Past or Current Illicit Drug Abuse
- Presence of Chronic Pain
- Number of Previous Onabotulinum Toxin A injection
- Previous Therapies for OAB (Lifestyle, Medication, Peripheral Tibial Nerve Stimulation, Sacral neuromodulation)

Source: The Participant Satisfaction Score, PHQ 9 score and GAD 7 score will be documented by the study coordinator into the case report forms and later transferred in the REDCap Data Management system. The participant demographics, co-morbid condition, current medications, smoking status, history of past or current illicit drug abuse, presence of chronic pain, number of previous Onabotulinum Toxin A injections, and previous therapies for OAB will be extracted from the electronic medical records. This information will be transferred to the REDCap Data Management System by the Principal and Co-investigators on the study.

4 Subject Selection Enrollment and Withdrawal

4.1 *Inclusion Criteria*

- Age 18 and older
- Scheduled to receive Intradetrusor Onabotulinumtoxin A injection
- English speaking

4.2 *Exclusion Criteria*

- Unable or Declining to Give Informed Consent
- Allergy to adhesives
- Participant self-report of previous use of TENS Unit within 1 year prior to study enrollment.
- Fitted with pacemaker or automatic implanted cardiac defibrillator
- History of Epilepsy
- Pregnancy and Postpartum period (within 12 weeks postpartum)

4.3 *Subject Recruitment, Enrollment*

All women with a diagnosis of Overactive bladder who are pursuing Office Cystoscopic Onabotulinum Toxin A for treatment and receiving care at the Division of Urogynecology, Mayo Clinic in Rochester, Minnesota will be approached for this study. Fellows, residents, Advanced level providers and Urogynecologists can offer these participants to talk with the study coordinator. The study coordinator will then be notified of women with Overactive Bladder interested in office based Cystoscopic Intra-detrusor Onabotulinum Toxin A injections by the care provider/Registered Nurse during the office visits following their appointment. The study coordinator will then approach the women interested in the study immediately following this appointment. The study coordinator will make sure that the participant meets the inclusion and exclusion criteria for the study. A written informed consent will be obtained from all eligible women who chose to participate using a standardized consent form approved by the Mayo Clinic Institutional Review Board. We will allow for 1 year from the start of recruitment for accrual of participants, expecting to enroll approximately 5 participants per month. A total of 60 participants will be recruited with 30 participants in each group (Active TENS group and Sham TENS group).

4.4 *Withdrawal of Subjects and Follow up*

A participant can chose to withdraw from the study at any point. A verbal request is all that is needed and can be conveyed to anyone of the team members taking care of the participant. This information will then be relayed to the study coordinator by the person receiving the request. No further follow up is needed.

5 Study Procedures

A flow chart of study activities is provided in Protocol Section 3.4

5.1 *Visit 1:*

Participants will be recruited from the Division of Urogynecology at Mayo Clinic, where care is being provided. Care providers will determine whether women are interested in learning about the study. The study coordinator will then be notified of women with Overactive Bladder interested in office based Cystoscopic Intra-detrusor Onabotulinum Toxin A injections by the care provider/Registered Nurse during the office visit following their appointment. The study coordinator will then approach the women interested in the study immediately following this appointment. A written informed consent will be obtained from all eligible women who chose to participate using a standardized consent form approved by the Mayo Clinic Institutional Review Board. We will allow for 1 year from the start of recruitment for accrual of participants.

5.2 *Outpatient Procedure Visit: Cystoscopic Onabotulinum Toxin A Injection*

On the day of the scheduled procedural visit, all participants will receive a Generalized Anxiety Disorder 7 (GAD -7) and Depression screening questionnaire (PHQ-9). Those women screening positive for anxiety (GAD 7 score ≥ 10) or depression (PHQ-9 score ≥ 10), will be offered referral to their primary care provider for further management. These women can continue to remain in the study and will not be excluded. In the same questionnaire, the participants will be asked "Have you ever experienced sexual abuse?" in order to assess for a history of sexual abuse. Participants will also be asked "Have you experienced chronic, unrelenting pain for 6 months or more duration?" in order to assess for a history of chronic pain.

Participants will be randomized to two groups using a computerized sequence generator based on permuted block randomization (1:1 allocation ratio) on the day of the procedure by the registered nurse (RN) taking care of the participant. Participants in Group 1 will receive an Activated TENS unit for pain control. Participants in Group 2 will have a Sham, inactive TENS unit for pain control. Both groups will be blinded to the type of TENS unit received. The nursing team taking care of the participant will know about the randomization. The care providers performing the procedure and the study coordinator will not be notified about the randomization.

On the day of the procedure, after baseline questionnaires and randomization, the participant will receive intraurethral lidocaine jelly as part of the standard pain control measures. Her bladder is then emptied using a Foley Catheter, and at the same time the bladder is then backfilled with 30 ml (300 mg/30 ml) of 1 % plain lidocaine solution. A waiting period of 30-50 minutes duration is allowed for the intravesicle lidocaine to take effect. During this wait period, participant is asked to lie supine for 10-15 minutes, then roll to the left side for 10-15 minutes and then to right side for about 10-15 minutes.

The participant, the provider taking care of the participant and the study coordinator assigned to the study will be blinded to the randomization. Both groups of participants will receive the TENS unit electrode placement during this wait period by the RN.

In participants randomized to the Active TENS group, the TENS unit will be initiated on standard setting (see 'TENS, Electrode Placement, and Settings') 5 minutes before starting the cystoscopy and will last the duration of the cystoscopy. The device intensity (amplitude) will be individually adjusted to each participant's maximum sensory level, which is the strongest reported tingling feeling without pain and muscle contractions and kept at this setting for the duration of the procedure.

Participants randomized to the Sham TENS group will not receive the TENS therapy. Instead, they will receive electrode placement followed by initiation of the TENS unit until the participant feels the tingling sensation, following which the TENS unit will be immediately turned off by the RN. The participant will be notified by the RN that the TENS stimulus has been turned down such that they are not able to feel the tingling sensation anymore.

Following the initiation/placement of the TENS unit, the study coordinator and fellowship trained Urogynecologist will enter the room. Rigid cystoscopic Intradetrusor Onabotulinumtoxin A injection will be performed by a fellowship trained Urogynecologist. This involves 100 units of Onabotulinumtoxin A injected in roughly 20 aliquots throughout the bladder. After the procedure participants are discharged home.

Care providers performing the injection will only be allowed into the procedure room once the TENS units has been activated. The nursing staff will assess the pad placement sites for any skin irritation, and or burns. If so, this will be documented on the participant's electronic medical record. The study coordinator will ask the participant and the provider separately (in the absence of the other) whether they felt the participant was in the Active TENS group versus the Sham TENS group at the end of the procedure. Participants will be advised to call and inform the clinic if they experience any burns, skin irritation or muscle soreness/pain.

5.2.1 TENS Unit, Electrode Placement and Settings

The nursing team will be provided with official training on the appropriate use of TENS unit, prior to its implementation. The nurse taking care of the participant will place the electrodes and manage the TENS unit. An iStim EV804 TENS unit along with 4 AUVON TENS self-adhering stimulating electrodes will be used for each participant.

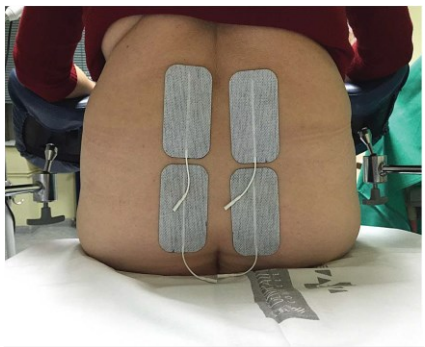

Figure 1: Electrode Placement
Lisón et al (2017). Pain Relief During Office Hysteroscopy. Obstet Gynecol

Electrode Placement: Two sets of two self-adhesive electrodes to be placed parallel to the spinal cord at the T10–L1 and S2–S4 levels as shown in Figure 1.

Activated TENS Output Parameters: Based on randomization the TENS unit will be either activated or left inactive (after a brief initial activation to avoid the unblinding of the participant) 5 minutes prior to and for the duration of the cystoscopic injection procedure. Active parameters are: asymmetric, balanced, biphasic square waveform at a mixed stimulating frequency that randomly varying between 80 and 100 Hz and a pulse duration of 300 microseconds.

5.3 *Masking/Blinding*

Participants in both arms of the study will be blinded to whether they received Active TENS unit or Sham TENS unit. Only the nursing team will be notified about the randomization. The care providers performing the procedure and the study coordinator will not be notified about the randomization. The study coordinator will ask the participant and the provider separately (in the absence of the other) whether they felt the participant was in the Active TENS group versus the Sham TENS group at the end of the procedure.

Schedule of Events		
Study Activity	**Visit 1** **Outpatient Clinic**	**Visit 2 Outpatient Procedure** **Cystoscopic Onabotulinum Toxin A Injection**
Screening and Informed Consent	X	
Depression and Anxiety Screen		X
Randomization		X
Numerical Pain Score assessment		X
Participant Satisfaction Assessment		X
Participant and Provider Perception regarding Arm of study		X

6 Statistical Plan

6.1 *Sample Size Determination:*

Based on our baseline preliminary data and the study 'Transcutaneous Nerve Stimulation for Pain Relief During Office Hysteroscopy' by Lison et al (2017)[6], power calculations were performed. As estimates of the mean and variance of the pain scale we used table 2 from the Lison et al (2017) study and our preliminary data. Group sample sizes of 27 and 27 achieve 80.53% power to reject the null hypothesis of equal means when the population mean difference is μ1 - μ2 = 4.0 - 2.0 = 2.0 with standard deviations of 2.0 for group 1 and 3 for group 2, and with a significance level (alpha) of 0.050 using a two-sided two-sample unequal-variance t-test. With a 10% possible dropout rate, we plan to have 30 participants in each of the study.

6.2 *Statistical Methods:*

6.2.1 Specific Aim #1: To assess whether the TENS units is effective for intraoperative pain management during office cystoscopic Intradetrusor Onabotulinumtoxin A in women with OAB.

We plan to compare participant reported pain using a 0-10 numerical pain scale at baseline, during and after cystoscopic intradetrusor onabotulinumtoxin A injection in participants randomized to active TENS units and placebo TENS units. We will compare the change in numerical pain scale from baseline to intraoperatively and intraoperatively to postoperatively between both groups.

Hypothesis: We hypothesize that there will be a clinically significant pain reduction in the Active TENS group.

Interpretation: Assuming that pain as measured is decreased in the Active TENS group when compared to the placebo TENS group, then we will accept our hypothesis. If not, we will perform a subgroup analysis of our data to see if certain groups of people that have better pain reduction with the Active TENs unit and an analysis of risk factors that might contribute to pain with Intradetrusor Onabotulinumtoxin A injection.

Power Calculation: Based on our baseline preliminary data and the study 'Transcutaneous Nerve Stimulation for Pain Relief During Office Hysteroscopy' by Lison et al (2017)(6), power calculations were performed. As estimates of the mean and variance of the pain scale we used table 2 from the Lison et al (2017) study and our preliminary data. Group sample sizes of 27 and 27 achieve 80.53% power to reject the null hypothesis of equal means when the population mean difference is μ1 - μ2 = 4.0 - 2.0 = 2.0 with standard deviations of 2.0 for group 1 and 3 for group 2, and with a significance level (alpha) of 0.050 using a two-sided two-sample unequal-variance t-test.

Data Analysis: The data will be analyzed using an intention-to-treat approach. In order to account for individual participant pain sensitivity profiles through the experiment, random effect longitudinal model will be adjusted to the data controlling by treatment and selected covariates at baseline.

6.2.2 Specific Aim # 2: To evaluate the effect of TENS units on participant satisfaction following cystoscopic intradetrusor onabotulinumtoxin A injection in women with OAB.

We plan to evaluate participant satisfaction on a 10 point Likert scale immediately after the procedure in participants randomized to activated TENS units and placebo TENS units.

Hypothesis: There will be a high level of participant satisfaction on a 10 point Likert scale in the active TENS group.

Interpretation: Assuming that the participant satisfaction as measured is high in the Active TENS group, then we will accept our hypothesis. If not, we plan to do a subgroup analysis to see if there are factors that contribute to higher participant satisfaction in certain groups of people in both the Active TENS and Placebo TENS group.

Data Analysis: The data will be analyzed using an intention-to-treat approach. Baseline differences between both groups will be analyzed using Cochran-Mantel-Haenszel test with an Alpha level of 0.05. Spearman rank correlation coefficients between Likert scales will be using to assess the strength of the relationship.

7 Safety and Adverse Events

7.1 *Definitions*

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event

An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event

Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include:

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant disability or incapacity

And/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

Other important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance include:

- Burns
- Skin Irritation
- Muscle Pain or Soreness

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

For this study, the study treatment follow-up period is defined as from enrollment to 1 week after receiving the cystoscopic Onabotulinum Toxin A injection.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values

No abnormal laboratory values are related to the administration of the TENS Unit

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

7.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse

events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

CTCAE Version 5.0 (November 27, 2017) will be used for classification and grading of Adverse Events:

[redacted]

7.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event section of the Case Report Form. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

7.3.1 Investigator reporting: notifying the Mayo IRB

The study coordinator will promptly report to the Principal Investigator and co- investigators of "any unanticipated problems involving risk to subjects or others" (UPIRTSO) as defined by the Code of Federal Regulations [45 CFR 46.103(b)(5) and 21 CFR 56.108(b)(1)]. The adverse events will be documented on the CRF and the data management system.

The investigator will review all adverse event reports to determine if specific reports need to be made to the IRB. The investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

Investigators will collect, assess, and report all adverse events that occur during a clinical trial. The investigators will review each event and ensure the appropriate information is added to the case report form (CRF). If the event is serious, the internal reviewer (as appointment by the Mayo Clinic Obstetrics and Gynecology Department Research chair) and the Mayo Clinic IRB must be informed within 24 hours of the occurrence of the event. Non-serious events will also be reported to the internal reviewer and the Mayo Clinic IRB sponsor through documentation on the CRF and database updates. Any adverse event will be reported to the Mayo IRB, in the manner prescribed by Mayo's policy. [IRB Policy Document No. 10049, Procedure for the Investigator]. Once reported, the Mayo Clinic IRB will determine what constitutes an unanticipated problem involving risk to subjects or others (UPIRTSO) and will report to appropriate institutional officials, OHRP, and other relevant Federal agencies as set forth in IRB Policy III.C.

Information collected on the adverse event worksheet (*and entered in the research database)*:

- Subject name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention*):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5**)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The relationship of an AE to the Investigational Drug is a clinical decision by the sponsor-investigator (PI) based on all available information at the time of the completion of the CRF and is graded as follows:

1. Not related: a reaction for which sufficient information exists to indicate that the etiology is unrelated to the study drug; the subject did not receive the study medication or the temporal sequence of the AE onset relative to administration of the study medication is not reasonable or the event is c1early related to other factors such as the subject's clinical state, therapeutic intervention or concomitant therapy.

2. Unlikely: a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide plausible explanations.

3. Possible: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but which could also be explained by concurrent disease or other drugs or chemicals; information on drug withdrawals may be lacking are unclear.

4. Probable: a clinical event including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (de-challenge): re-challenge information is not required to fulfi1 this definition.

5. Definite: a reaction that follows a reasonable temporal sequence from administration of the drug, or in which the drug level has been established in body fluids or tissues, that follows a known or expected response pattern to the suspected drug, and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure (re-challenge).

The maximum intensity of an AE during a day should be graded according to the definitions below and recorded in details as indicated on the CRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates.

1. Mild: AEs are usually transient, requiring no special treatment, and do not interfere with patient's daily activities.

2. Moderate: AEs typically introduce a low level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.

3. Severe: AEs interrupt a patient's usual daily activity and traditionally require systemic drug therapy or other treatment.

7.1 Stopping Rules

An interim analysis will be performed after 30 participants have undergone cystoscopic Onabotulinum Toxin A injection as part of the study. The information will also be sent to an internal reviewer (as appointment by the Mayo Clinic Obstetrics and Gynecology Department Research chair). At this point a meeting between the investigators and internal reviewer will be convened to discuss the existing data, the efficacy and any safety issues including serious adverse events that have taken place. A decision will be made as to whether to continue with the study or to prematurely terminate the study based on any safety issues.

If there are greater than 3 serious adverse (i.e. severe skin reactions, burns, muscle weakness) events reported in the 30 participants reviewed, further recruitment and administration of the TENS unit will be stopped. The study will be put on hold with the IRB and each of the adverse events will be carefully looked into for any causal relation to the TENS unit. If no causal relationship is proved then the will re-approach IRB for restarting the study.

7.2 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

7.2.1 Internal Data and Safety Monitoring Board

An internal reviewer with Urogynecolgic expertise will be appointed by the Obstetrics and Gynecology Research Chair who will participate in review of any serious adverse events associated with the trial. A meeting convened with the internal reviewer will be performed after 30 participants have undergone cystoscopic Onabotulinum Toxin A injection as part of the study.

8 Data Handling and Reporting

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

8.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Original documents and data records include but are not limited to: hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

8.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded in the RedCaps Database. All missing data will be explained.

8.3.1 Data Management

Any data not collected on a study case report form will be manually abstracted from the electronic medical record and recorded in the Data Management System by the Principal and Co-Investigators.

8.3.1.1 Data Processing

The REDCap Data Management System will contain information captured from the Case Report Form and from the Electronic Medical Records. The Data Management system will be reviewed once a month by the investigators and the study coordinator for missing information. If missing data is noted in the data management system that can be captured from the Electronic Medical Records, the electronic medical records will be reviewed to capture this information.

8.3.2 Data Security and Confidentiality

Collected study data collected on case report forms will recorded in pen and will be stored in restricted access areas when not actively being used in the study. Only necessary research team members will have access to the data for data entry or analysis. All data collection and analysis will be performed behind the Mayo firewall.

8.3.3 Data Quality Assurance

The Case Report Forms will be cross checked by the study coordinator for completion at the end of the 24 hours after cystoscopic Onabotulinum Toxin A injection. At the completion of the study, the data in the Case Report Forms will be crossed with the data entered into the RedCaps Data Management System for accuracy. For the data entered from the electronic medical records into the Data Management System, a second Co-investigator will be assigned to randomly select a patient monthly and review the data entered into the Data Management System from the Electronic Medical Records.

8.3.4 Data Clarification Process

The case report forms will be checked for missing data before the patient leaves home from their procedure visit.

8.4 *Records Retention*

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

Subject-specific data and Case Report Forms will be identified by the patient medical record number and a unique coded number given to it; the patient name will not be included. The subject identification list will be stored behind the Mayo firewall.

Subject names and other directly identifiable information will not appear on any reports, publication, or other disclosures of clinical study outcomes.

The sponsor-investigator will retain the specified records and reports:

1. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy"

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all study-related documents, study related facilities (research pharmacy), and has adequate space to conduct the monitoring visit.

9.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, inspections by the IRB, and government regulatory agencies, of all study related documents. The investigator will ensure the capability for inspections of applicable study-related facilities (research pharmacy).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

10 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

This study does not involve any vulnerable populations.

11 Study Finances

Planned source of funding is the fellow research fund from the Division of Urogynecology, Mayo Clinic, Rochester, Minnesota allotted.

12 Publication Plan

The primary responsibility for publication is in the hands of the principal investigator and co-investigators. Permission will be needed from the primary responsible party before any information can be used or passed on to a third party. The study will be registered in ClinicalTrials.gov and the results will be posted to ClinicalTrials.gov within 12 months of final data collection for the primary outcome.

13 References

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