Sacral Neuromodulation in Dual Incontinence: Ultrasound and Afferent Nerve Sensation Assessment

(SaNDI)

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Synopsis

Title	Sacral Neuromodulation in Dual Incontinence: Ultrasound and Afferent Nerve Sensation Assessment
Short Title	SaNDI
Protocol Date	July 7, 2014
Study Duration	1.5 years
Study Center(s)	Northwestern University Feinberg School of Medicine
Objectives	1) To quantify the effect of sacral neuromodulation (SNM) on afferent innervation using current perception thresholds (CPT) in women with dual incontinence (urgency urinary incontinence (UUI) and fecal incontinence (FI)). 2) To identify neurophysiologic predictors of successful SNM in women with dual incontinence. 3) To quantify and compare baseline urethral and anal sphincter anatomy as assessed by ultrasound in women with dual incontinence who undergo successful and unsuccessful SNM. 4) To assess the quality of sexual relationships in women with dual incontinence and their male partners and to identify specific areas of dysfunction that are common in these patients.
Number of Subjects	30
Diagnosis and Main Inclusion Criteria	Women with responses of at least "*moderate bother" to PFDI-20 items 10 'do you lose stool beyond your control if your stool is loose or liquid*" and 16 "*do you experience urine leakage associated with a feeling of urgency that is a strong sensation of needing to go to the bathroom*" will be identified through routine screening in our multidisciplinary clinic. **Inclusion criteria:** Women over the age of 18 with idiopathic dual incontinence planning to undergo placement of a sacral nerve modulator and will be included if they have at least 5 UUI episodes on a 3-day diary and 2 FI episodes on a 7-day diary.

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1.0. INTRODUCTION - BACKGROUND AND RATIONALE

1.1 Introduction

One in four women reports bothersome symptoms of a pelvic floor disorder with 16% reporting urinary incontinence (UI)[1]. Likewise, 1 in 5 women with UI reports fecal incontinence (FI). Women with dual incontinence (UI/FI) often have more bothersome symptoms, quality of life impact, and sexual dysfunction than those with just UI or FI. Sacral neuromodulation is the only currently available treatment with Level 1 effectiveness data for BOTH UUI and FI. Yet, the precise mechanism of action of SNM on UI and FI is unclear. Alterations in both afferent innervation and muscular function are believed to play a critical role in etiology of UI and FI as well as patient's response to various treatments. This study aims to use innovative techniques to further our understanding of the neural and muscular alterations associated with dual incontinence AND identify potential neuromuscular mechanisms to guide treatment success. We will also study the impact of dual incontinence on sexual function in women and their partners. While many investigators have attempted to describe sexual function in women with UI and FI, few have addressed the impact the disorders may have on their partner's.

1.2 Background and Significance

1.2.1 Impact of UUI/FI on Quality of Life & Sexual Function

At least 1 in 5 women reports bothersome urgency urinary incontinence (UUI) and/or fecal incontinence (FI) with even higher prevalence rates among the elderly[1,2]. In a large, national recent cross-sectional analysis, nearly 25% of women reported bother from at least one pelvic floor disorder[1]. Urgency urinary incontinence and FI each can impact women's quality of life; however, the combination of both UUI and FI often results in even more dramatic effects on a woman's quality of life[3]. Urinary urgency incontinence affects women's sexual function, which often improves after treatment[4]. Likewise, FI causes mental burden and emotional frustration and is also associated with decreased sexual function [5,6]. Although many studies evaluate SNS treatment efficacy and ability to improve quality of life, few have assessed adequately assessed sexual health. The complex relationships between urinary incontinence and a woman's self image, sense of well being, sexual activity, and sexual function is well established, and one can only assume the impact of FI or dual incontinence would be even more dramatic[7,8]. Sexual dysfunction in the context of a relationship is a shared dysfunction.

Female partners of men with erectile dysfunction demonstrate high levels of sexual dysfunction[9]. It is reasonable to suspect UUI and FI in women have an impact on the sexual function of their male partners[9,10].

1.2.2 Pathophysiology of UUI/FI and Mechanism of Action of SNM

The etiologies of UUI and FI are complex and likely multifactorial; however, increasing data suggests neuromuscular dysfunction, particular alterations in afferent nerves, plays a role in both. SNM has proven effective for treatment of UUI and FI[11,12]. Electrical stimulation is thought to modulate afferent nerves and reflex pathways, which in turn influence urinary and fecal continence mechanisms. The exact mechanism of SNM for the treatment of UUI and FI remains unclear and few data exist to guide which patients will respond to therapy. Further characterization of neural function of patients who undergo successful SNM may provide insight into appropriate patient selection as well as advance our understanding of pathophysiology of incontinence and SNM treatment.

A systematic review evaluating SNM in the treatment of lower urinary tract dysfunction, concluded SNM was clinically effective (>50% improvement) in 60-90% of women with UUI[13]. Similarly, a multi-center trial demonstrated SNM success rates of 90% for women with FI (>50% reduction in FI episodes)[11]. Fecal incontinence symptoms improved in 49% of women with dual incontinence who underwent SNM primarily for UUI[14].

Although SNM successfully improves UUI and FI in some women, there are no reliable predictors of successful symptoms resolution with SNM[15,16]. Women > 55 and/or with >3 co-morbid conditions have lower UUI cure rates following SNM[15], however, clinical phenotypes of women who *will* respond to SNM are unknown. Identification of quantifiable afferent neural and sphincter muscular parameters associated with successful SNM will aid patient selection as well as further understanding of pathophysiology of UUI/FI and mechanism of action of SNM in treating these disorders. This novel approach is the first to quantify objective afferent neural function with validated clinical measures and 3-dimenstional ultrasound assessments of both the urethral and anal sphincters in women with dual incontinence.

1.3 Preliminary Work

Our team has extensive expertise and experience in neurophysiologic testing of the pelvic floor in women with urinary incontinence[17]. We showed improvement in urethral afferent sensation using CPT in women with UUI treated with tolterodine[18]. Urethral afferent sensation at stimulation frequencies corresponding to A-δ and C fibers improved after treatment, suggesting anticholinergic medications modulated urethral afferent innervation.

Urethral morphology using 2-D US is different in women with detrusor overactivity

compared to controls[19,1]. We recently demonstrated that urethral sphincter complex was easily and reproducibly quantified using 3-D US in women with UI[20].

1.4 Innovation

1.4.1 Sensory Nerve Testing: Urethral and Anal Sphincters

Current Perception Threshold testing is a neurophysiologic test that uses electrical stimulation in the lower urinary tract to further clinical investigation of afferent innervation in pelvic floor dysfunction[21,22]. CPT testing reliably uses electrical stimuli at varying frequencies to activate different subpopulations of afferent nerve fibers[21]. A constant current electrical stimulator delivers sine wave stimuli at three different frequencies, which selectively depolarize different types of sensory nerves based on variations in membrane ion channel concentration. Large myelinated A- β fibers are stimulated at 2000 Hz, smaller myelinated A- δ are stimulated at 250 Hz and unmyelinated C fibers are stimulated at 5 Hz. In vivo, A- δ fibers are activated by increased tension on the bladder wall and C-fiber activation is associated with some pathologic states[23-25]. Multiple authors described CPT testing in the bladder and/or urethra of women with lower urinary tract problems[26-28]. The use of CPT testing in the anus will be a novel approach to evaluate the afferent nerve function of the anus. We hope that afferent nerve function assessment can be a useful predictor of those women who will positively respond to SNM for the treatment of dual incontinence. This would alter treatment algorithm for women with UUI and FI and might potentially save women from undergoing an invasive procedure that is unlikely to improve their incontinence.

1.4.2 3-Dimentional Ultrasound Imaging: Urethral and Anal Sphincters

Ultrasound imaging of the internal and external anal sphincter as well as puborectalis are part of routine clinical care in women with FI. In fact, ultrasound evidence of sphincter defect has been associated with more severe disease[29]. Likewise, urethral morphology using 2-D ultrasound is different in women with detrusor overactivity compared to controls. The urethral longitudinal smooth muscle thickness was decreased in women with detrusor activity[19] suggesting that anatomic changes in urethral sphincter may be associated with UUI.

This proposal is highly innovative in that it addresses two common theories for etiology of UUI and FI in women: neural and muscular disruption. This study will capture 3-dimentional ultrasound imaging and measure small fiber afferent innervation to both the urinary and anal sphincter muscles. We will be able to determine associations

and relationships between sphincter size/volume and afferent nerve function in both the anal and urethral sphincters, which may further our understanding of the complex etiology of these disorders and aid in predicting treatment outcomes.

2.0 OBJECTIVES

2.1. Primary Objectives:

2.1.1. To quantify the effect of sacral neuromodulation (SNM) on afferent innervation using current perception thresholds (CPT) in women with dual incontinence (urgency urinary incontinence (UUI) and fecal incontinence (FI)).

2.2. Secondary Objectives:

2.2.1. To identify neurophysiologic predictors of successful SNM in women with dual incontinence.

2.2.2. To quantify and compare baseline urethral and anal sphincter anatomy as assessed by ultrasound in women with dual incontinence who undergo successful and unsuccessful SNM.

2.2.3. Women who undergo successful SNM will have larger urethral and anal sphincter muscles.

3.0. SELECTION OF SUBJECTS

3.1 INCLUSION CRITERIA

3.1.1. Subject is a female over the age of 18 years old
3.1.2. Subject is diagnosed with idiopathic dual incontinence
3.1.3. Subject is planning to undergo placement of a sacral nerve modulator
3.1.4. Subject has at least 5 UUI episodes on a 3-day diary
3.1.5. Subject has 2 FI episodes on a 7-day diary
3.1.6. Subject has given signed, informed consent prior to registration on study

3.2 EXCLUSION CRITERIA

3.2.1. Subject has a neurologic disease
3.2.2. Subject has a disease that may impair sphincter tone or sensation
3.2.3. Subject is pregnant
3.2.4. Subject has > Stage II pelvic organ prolapse

3.2.5. Subject underwent rectal surgery in the past year
3.2.6. Subject has chronic inflammatory bowel disease
3.2.7. Subject has diathermy
3.2.8. Subject has QTc prolongation
3.2.9. Subject has cardiac arrhythmia
3.2.10. Subject has other contraindication to SNM.

4.0 SUBJECT REGISTRATION

The Women's Integrated Pelvic Health Program (IPHP) of Northwestern Medicine and Prentice Women's Hospital is a multidisciplinary center with urogynecologists and colon and rectal surgeons specializing in pelvic floor disorders. Women are referred for comprehensive, interdisciplinary evaluation and treatment. Consecutive women undergoing SNM for dual incontinence will be approached for study participation. Consenting participants will complete the short form of the Pelvic Floor Distress Inventory (PFDI-20) as well as 3-day urinary and 7-day bowel diaries to determine eligibility. Women with responses of at least "moderate bother" to PFDI-20 items 10 '*do you lose stool beyond your control if your stool is loose or liquid*" and 16 "*do you experience urine leakage associated with a feeling of urgency that is a strong sensation of needing to go to the bathroom*" will be identified through routine screening in our multidisciplinary clinic.

4.1. Informed Consent (IC) and Institutional Review Board (IRB)

4.1.1. Subject Informed Consent

The Study Coordinator and Principal Investigator will write the Subject Informed Consent Form based off a Northwestern University approved template. The Subject Informed Consent document to be used in this study must be submitted to and approved by the Investigator's IRB prior to screening any potential subjects. Any revisions to the written Informed Consent Form should receive IRB approval in advance of use.

The Site is responsible for obtaining Informed Consent for each subject by having them sign the Subject Informed Consent Form **prior** to performing any test specifically for this study or collecting any data specific to this study. Informed consent will be obtained from the woman participating in the study as well as her partner, who will be filling out questionnaires. Study specific activities include:

- Current Perception Threshold Testing
- GRISS Questionnaire

- FiQOL Questionnaire

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

We will waiver the documentation of consent process for the male participants in this study. Their only requirement for participation in this study is to complete a questionnaire, which will be administered to them via an online survey through RedCAP, a secure data capture platform. They will receive an email containing the link to the survey, and the body of the email to the male participants will include an online consent document. The male participant will read through this consent and have the option to voluntarily complete the survey, or not to complete the survey by exiting out of the email. We will keep the written consent forms for males that do not have internet or email access.

4.1.2. Institutional Review Board

The IRB is responsible for safeguarding the rights, safety, and well being of all subjects. It is the responsibility of the Investigator to submit all required documentation to the IRB including the Investigational Plan and Subject Informed Consent Form. Written documentation of approval of the Investigational Plan and Subject Informed Consent Form must be provided to the Sponsor **before** starting the registry.

5.0 STUDY DESIGN & METHODS

Summary of Study Design:

	Baseline	***Test phase***	***3 month follow-up***
Bladder/bowel diary	*X*	*X*	*X*
Multichannel urodynamics	*X*		
Endovaginal and endoanal ultrasound	*X*		
CPT testing	*X*		*X*
PFDI	*X*		*X*
FISI	*X*		*X*
FiQOL	*X*		*X*
PISQ-IR	*X*		*X*
GRISS	*X*		*X*

5.1. Pre-Treatment Evaluation/Baseline

Once the participant and her partner consent, they will undergo a standardized assessment. After the completion of the CPT testing and filling out the required surveys, the participant

will receive a $50 Prepaid gift card at this initial baseline visit.

5.1.1. Data Collected:

5.1.1.1. Age
5.1.1.2. Race/Ethnicity
5.1.1.3. Medical Co-morbidities
5.1.1.4. Prior UUI or FI treatments
5.1.1.5. Parity
5.1.1.6. Prior Surgery

5.1.2. Standardized Physical Examination Tools:

5.1.2.1. Pelvic floor muscle strength using the Oxford scale
5.1.2.2. Quantification of pelvic organ prolapsed using POPQ
5.1.2.3. Anal Sphincter Tone

5.1.3. Other Examinations Performed

5.1.3.1. 3-D Endovaginal ultrasound

3-D endovaginal ultrasound will be performed using a BK 8838 12mHz, 360degress rotational transducer (BK Medical, Herlev, Denmark). Women will come in with a comfortably full bladder. In dorsal lithotomy, the ultrasound probe will be inserted into the vagina without excessive pressure. The correct anterior-posterior orientation will be noted using the hyperechogenic aspect of the pubic bone which will be designated the 12 o'clock position, with the anal canal at the 6 o'clock position. The operator will hold the transducer still during the image acquisition that will be performed at a length of 6 cm to scan for 60 seconds. This will yield a 3-D rendered cube to measure the urethra sphincter. This technique has previously been demonstrated[30,31]

5.1.3.2. 3-D Endoanal ultrasound

3-D Endoanal ultrasound will be performed with a BK 2052 360degress rotational transducer (BK Medical, Herlev, Denmark). Prior to the endoanal ultrasound exam, women will undergo a digital rectal exam to estimate the orientation of the anal canal. In the dorsal lithotomy position the probe is introduced along the axis of the anal canal until the puborectalis muscle sling is visualized. The anal canal, is divided into three sonographically distinct levels: high, mid, and low. The 3-D rendered cube is obtained at the level of the high anal canal for measurement[32].

5.1.3.3. Multichannel urodynamic testing:

All women will undergo standard urodynamic studies according to International Continence Society guidelines.

5.1.3.4. Current Perception Threshold Testing*:

Subjects will undergo CPT testing in a standardized fashion using a Neurometer CPT device in the dorsal lithotomy position. The 2000 Hz frequency will be tested first using the method of limits technique. Next, the amplitude is slowly increased until the stimulus is perceived. This is recorded as the upper limit. Then the stimulus is turned off until the initial sensation subsides. The same stimulus is then slowly decreased until the patient no longer perceives the stimulus. The last stimulus the patient can perceive is termed the lower limit. The upper and lower limits are then averaged to obtain the sensory threshold by the method of limits. The subject is then given a series of forced choice tests by the Neurometer to determine the sensory threshold by the method of levels starting at the lower limit obtained by the method of limits. The Neurometer randomly picks real and false stimuli separated by a 3–5 second rest period. The subject indicated which stimulus was stronger as the intensity was decreased by 0.4μA increments. Both the method of limits and the method of levels are then repeated at 250 Hz and 5 Hz.

5.1.4. Questionnaires and Surveys Administered

5.1.4.1. Pelvic Floor Distress Inventory (PFDI-20)[33]:

A validated, condition-specific pelvic symptom questionnaire for quantification of pelvic symptoms

5.1.4.2. Fecal Incontinence Severity Index (FISI)[34]:

A validated questionnaire designed to capture the severity of fecal incontinence symptoms.

5.1.4.3. Pelvic Organ Prolapse Incontinence Sexual Questionnaire, IUGA-revised (PISQ-IR)[35]:

A validated condition-specific female sexual function questionnaire developed to assess sexual function in women with pelvic floor dysfunction.

5.1.4.4. Golombok Rust Inventory of Sexual Satisfaction (GRISS)[36]:

A questionnaire developed by sex therapists in the UK in the 1970s for the assessment of the existence and severity of sexual problems[39]. It can be used to

assess the quality of the sexual relationship of a couple and of an individual's function within a relationship. The GRISS is designated as Grade A (highly recommended) by the Fourth International Consultation on Incontinence. It is easily self administered, allowing for privacy for subjects completing the survey. It takes approximately 15 minutes to complete. The GRISS consists of seven domains, five of which are shared (Non-communication, Infrequency, Dissatisfaction, Avoidance, Non-sensuality) and two of which are gender specific (Vaginismus and Anorgasmia for women, Impotence and Premature Ejaculation for men). Raw scores are transformed to a scaled scores ranging from 1 to 9, with higher scores indicating greater sexual dysfunction. A range of 1 to 4 is considered non-problematic and scores greater than or equal to five are consistent with dysfunction. It is expected that a "normal", functional relationship will yield at least one score of 5 on one of the domains. For this analysis, a score of 5 or more in any category was considered to be consistent with sexual dysfunction.

5.1.4.5. 3-day urinary and 7-day bowel diary

5.1.4.6. Fecal Incontinence Quality of Life Questionnaire:

A validated questionnaire assessing the impact of fecal incontinence on one's quality of life.

5.2. Stage I Procedure – Test Phase

Study participants will undergo a staged implant procedure as previously described[37,38]. A quadripolar electrode (Medtronic) will be placed into the sacral foramen (confirmed with fluoroscopy) and connected via a percutaneous extension kit (Medtronic) to an external test stimulator (Medtronic) for approximately 7 days. During the test period, patients will record bladder and bowel diaries. If the number of incontinence episodes is reduced by 50% the patients will undergo placement of a permanent device, InterStim (Medtronic, Minneapolis, MN).

5.3. Stage II Procedure – Permanent Device Implantation

During Stage II, the patient will undergo implantation of the permanent sacral neuromodulator, InterStim, if symptoms showed 50% improvement during the test phase. This will require a 2-3 day stay in the hospital and will be performed under general anesthesia.

5.4. Three Month Follow up Visit

At the time of this visit, patients who did receive the implanted InterStim will receive an additional $50 Prepaid gift card for undergoing CPT Testing and filling out surveys at the 3 month follow up visit.

5.4.1. Questionnaires and Surveys Administered

5.4.1.1. Pelvic Floor Distress Inventory (PFDI-20)[33]
5.4.1.2. Fecal Incontinence Severity Index (FISI)[34]
5.4.1.3. Pelvic Organ Prolapse Incontinence Sexual Questionnaire, IUGA-revised (PISQ-IR)[35]:
5.4.1.4. Golombok Rust Inventory of Sexual Satisfaction (GRISS)[36]:
5.4.1.5. 3-day urinary and 7-day bowel diary
5.4.1.6. Fecal Incontinence Quality of Life questionnaire (FiQOL)

5.1.4.2. Other Examinations Performed

5.1.4.2. Current Perception Threshold (CPT) Testing

6.0. STATISTICAL PLAN

6.1. Statistical Analysis:

Each sensory modality threshold as determined at each of the different anatomic sites will be evaluated separately. Sensory thresholds will be compared before and after SNM placement using paired t-test. Multivariate regression models will be used to determine clinical and neurophysiologic predictors of symptom improvement. Urethral sphincter volumes and presence/absence and size of internal and external anal sphincter defects will be compared in responders and non-responders.

6.2. Sample Size Determination:

The sample size estimate was based off data from our prior work and urethral CPT in women with overactive bladder symptoms before and after treatment of tolteradine . Assuming a mean urethral CPT of 1.3 at 250 Hz prior to treatment and a mean of 0.75 after treatment with a standard deviation of 0.66 we estimate that 13 subjects are needed to show a significant difference with a 80% power at 5% significance level. Assuming a 20% dropout rate, we will recruit 15 women and their partners.

7.0. DATA COLLECTION & RECORD KEEPING

7.1. Data Collection:

7.1.1. General Data Recording Instructions

Data Collection will occur in accordance with the registry specific monitoring and data management plans and will follow established SOPs. A combination of web-enabled and centralized data management will be used. Data will be collected into an online Data Capture program called REDCap. This is a secure, web-based application used for the management and collection of data from surveys and questionnaires that are used in this study. This program will also help with the analysis and scoring of the data entered by the patients into the questionnaires and surveys. Reasons for missing data should be documented on the appropriate case report form.

7.2. Record Retention

Participating Investigators/sites shall maintain accurate, complete, and current records relating to the participation in a safe and secure area:

- All correspondence with other Investigators/sites, or IRB.
- Approved protocols and approved Informed Consent Forms.
- Subject specific case report forms and supporting data including, signed and dated Consent Forms and medical records including; progress notes of the physician, the information and data on the condition of each Subject upon entering, and during the course of, the investigation, information about relevant previous medical history and the results of all diagnostic tests.

Any paper documentation will be kept in a locked cabinet, separate from other study documents. Following completion of the study, all linking documents will be deleted from the hard drive and hard copies placed in a HIPPA approved container for shredding.

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