Project Title
Feasibility of home parasacral transcutaneous electrical nerve stimulation for voiding dysfunction in the pediatric population – a pilot study

NCT ID Number: 117756

Principle Investigators
Glen Lau, MD, Anthony Schaeffer, MD

Co-Investigators
DeeAnn Cervantes, NP, AnnMarie Hannon, NP, Heidi White, NP, Neha Malhotra, MD

Document Date
January 23, 2019

Background/Justification

Overactive bladder (OAB) is the most common voiding dysfunction in children[1]. While many children may outgrow these issues, for some these symptoms persists and can lead to emotional, social, behavioral and physical problems. Multiple treatments exist for OAB but rarely is there guaranteed success. Many behavioral and lifestyle treatments involve a significant time investment and office visits on the part of the patient and family. Furthermore, medication therapy is often associated with bothersome side effects and is discontinued, even despite efficacy[2]. As such, treatments with potentially less adverse effects, often used in adult urology, are making their way into the pediatric urology practice. These include intravesical botulinum toxin injections, sacral nerve stimulation (SNS) and percutaneous tibial nerve stimulation (PTNS).

PTNS, first cleared by the United States Food and Drug Administration (FDA) in 2011 for adult use, has evolved into transcutaneous nerve stimulation in the pediatric population; obviating the need for needles during treatment. Studies suggest mixed efficacy in electric nerve stimulation for overactive bladder in the pediatric population, owing largely to the marked heterogeneity in treatment protocols. While some researchers follow the traditional tibial nerve pathway, others take a cue from SNS and target the parasacral area, while still others rely on signaling from even further peripheral nerves to modulate bladder overactivity [3-5]. Perhaps further contributing to the disparate data is the varying treatment schedules used. Some centers perform treatments daily, others weekly, others twice or thrice a week. Similarly, some physicians recommend twenty-minute treatments, while others thirty or even sixty minutes. The majority of studies rely on an office-based treatment model, while a few have explored in home treatments[3-5]. In the United States, there has been no study examining the feasibility or efficacy of home parasacral transcutaneous electric nerve stimulation (PTENS) on pediatric voiding dysfunction.

Definitions

Terminology adheres to the standards recommended by the International Children's Continence Society (ICCS) except where specifically noted[6].

Bowel and bladder dysfunction (BBD) concomitant bladder and bowel disturbances – does not explain etiology but describes parallel dysfunction

Lower urinary tract dysfunction a term encompassing many times of urinary dysfunction (see below) in children older than 5; excludes bowel dysfunction

Increased voiding frequency ≥8 voids per day; may be subjectively described as fewer than 8 voids

Incontinence involuntary leakage of urine; includes continuous and intermittent incontinence – continuous incontinence is typically associated with an anatomic abnormality

Daytime incontinence intermittent incontinence that occurs while awake

Enuresis intermittent incontinence that occurs exclusively during sleeping periods; though enuresis is sometimes used to refer to daytime incontinence, the ICCS definition specifies nocturnal

Urgency sudden and unexpected experience of an immediate and compelling need to void

Overactive bladder condition in which a child experiences urgency symptoms; may or may not be associated with incontinence; replaces the term bladder instability[7]

Nocturia waking at night specifically to void; distinct from enuresis, in which the child is incontinent during sleep

Specific Aims

Primary Aims

1. To examine feasibility (adherence) of thrice weekly, thirty minute home treatment sessions
2. To evaluate recruitment into a randomized trial for pediatric voiding dysfunction

3. To refine, if needed, treatment protocol for both study and control groups
4. To estimate effect size, with point estimates and confidence intervals, of treatment and control groups

Secondary Aims

1. To confirm safety and identify potential adverse events with use of in-home PTENS
2. To identify possible barriers to in-home PTENS
3. To compare the efficacy of in-home, PTENS to traditional behavioral therapy on parameters of urinary voiding dysfunction in the pediatric population
4. To explore efficacy of in-home, PTENS to traditional behavioral therapy on parameters of bowel dysfunction in the pediatric population

Recruitment Methods

Participants will be recruited through the Primary Children's Urology Clinic by nurse practitioners. Patients and families of patients with diagnoses of enuresis or daytime incontinence (ICD-10 R32), bladder instability (ICD-10 N32.89), bladder dysfunction (N31.9), nocturnal enuresis (N39.44), nocturnal and diurnal enuresis (ICD-10 N39.498), urinary frequency (ICD-10 R35) and urinary frequency (ICD-10 R39.15), who meet inclusion criteria, will be counseled on possible study enrollment by the primary treating nurse practitioner. Clinic schedules, with reason for visit, will be queried twice weekly by study coordinators (non-clinical personnel) to identify potential subjects based on keywords including incontinence, dysuria, urinary tract infection (UTI), enuresis, wetting, urinary retention, incomplete emptying, voiding dysfunction and dysfunctional voiding. Providers will be given a list of potential subjects. Subjects will be randomly assigned into either treatment or control by study coordinators using an electronic randomization function using Research Electronic Data Capture software (REDCap). Patients and families will be asked no more than once to consider participation in the study. A potential patient list, screening log and patient numbers will be kept in a secure file on a secure drive on the University of Utah servers.

Sample Size

Based on prior work in examining continuous variables for averages and variability during pilot studies, the recommended sample size per group is 12 subjects[8]. To account for attrition, 15 subjects will be randomized to each group.

Characteristics of Participants

Inclusion Criteria

Toilet trained (>age 6) to age 18

Diagnosis of urinary dysfunction, voiding dysfunction, overactive bladder, urgency incontinence, nocturnal enuresis

Exclusion Criteria

Known neurologic diagnosis – such as myelomeningocele, caudal regression
Known seizure disorder
Age < 6 or > 18
Lack of follow-up within 6 months of treatment
Pacemaker, vagal nerve stimulator, or other implanted electrical device
Intolerance of electrical nerve stimulation
Pregnancy
Implanted metal hardware
Open sores or wounds over the sacral area

Currently catheterizing for bladder drainage
Known anatomic lower urinary tract abnormality (may be congenital or iatrogenic)
Bowel only voiding dysfunction (Constipation ICD-10 K59.00)
Non-English speaking families
Families with health literacy precluding completion of questionnaires and voiding diaries
Concurrent use of anticholinergics, alpha blockers or beta agonists for urologic treatments
Untreated urinary tract infection

Summary of Methods

At the initial visit all subjects will complete a Dysfunctional Voiding Symptom Score (DVSS) and be given a packet on controlling overactive bladder and pediatric enuresis (see Appendix 1). All subjects will then complete a 48-hour voiding diary, a nighttime wetting log (at home), a urinalysis and culture, a renal and bladder ultrasound, a non-invasive uroflowmetry test and they will watch short videos on daytime and nighttime wetting as well as constipation in children. (All items at this visit are standard of care) They will also complete a medical colon cleanout using polyethylene glycol and senna, as is the current clinic standard of care.

In 4-6 weeks, after all testing is completed, all subjects will follow-up for review of these testing results. (This follow-up visit is considered standard of care). Patients who had a positive urine culture or other abnormalities found on ultrasound or uroflowmetry that suggest an anatomic obstruction will be excluded from this research study.

Subjects who are still eligible to participate will then be randomized, at the same office visit, using an online randomization tool to either standard behavioral therapy (control) or standard behavioral therapy in addition to the PTENS device. Subjects will then be instructed on standard behavioral therapy or standard behavioral therapy in addition to PTENS (see Appendix 2). This randomization is for research purposes only.

Subjects will then be contacted weekly by study personnel to assess and document treatment adherence as well as identify any potential adverse events. (Research Purposes Only)

In 6 weeks, subjects will complete (at home) a voiding diary, a wetting log and a DVSS. These will be transmitted to the office through secure e-mail and uploaded into the chart. (Research Purposes Only)

In 12 weeks, subjects will follow-up in clinic with repeat voiding diary, wetting log and DVSS for further assessment and discussion of treatment adherence, barriers to adherence and adverse events, if any. (This visit is standard of care and would occur regardless of the patient participating in the research study)

Risks and/or Ethical Issues

Based on previous data, there is a risk of minor skin irritation or redness at the application site[9], and families will be informed of this prior to initiation of treatment and be instructed to discontinue treatment if this occurs. Previous studies have shown this risk to be <20%[9]. This can be prevented by correct placement and adherence to recommended treatment[10]. Other foreseeable risks may be pain at the site of electrode application. No serious side effects have been reported[10]. There is a risk of psychological stress (some children may experience frustration with the length of the treatment or with the process itself) of treatment. This will be monitored throughout the study period.

There is a risk of loss of confidentiality. Data will be obtained from the medical record and patient encounters and be maintained on case report forms that will be stored in a locked office. This data will be entered into REDCap. REDCap is a HIPAA-compliant, secure database that restricts access to study data based on user roles and permissions. Patient list will be kept in a password-protect file, on a password-protected desktop computer, in a locked office.

There is a potential ethical issue of continuing inferior treatment. If interim analysis reveals clear superiority of one treatment type or schedule, other study participants will be offered the superior treatment option.

Benefits
Subjects may benefit from this study in improvement in their lower urinary tract symptoms.

Informed Consent Process
IRB compliant informed consent from parents (or guardians) will be undertaken and documented (See Appendix 3). Assent for children will be obtained as age appropriate.

Measures to Protect Privacy and Confidentiality of Participants
The confidentiality of all patient information will be maintained and all guidelines set forth by HIPAA and the IRB will be strictly adhered to. All patient data will be stored on either in a password-protected file, on a password-protected desktop computer in a locked office, case report forms in a locked office, or electronically in REDCap on a secure server. Any information used in statistical analysis will be de-identified. No identification of patients will be made in any presentations or publications related to this study

Timetable
Pilot study and data gathering will be undertaken over the next three months (January 2019 – March 2019). One month will be given to analyzing the feasibility, designing and randomized trial and completing the IRB process. Once pilot study has been completed and analyzed, this data will be used to refine and complete a larger scale randomized control trial. Plan will be for study to take place over a six-month period, estimated to be Summer through Winter of 2019.

Data Management of Statistical Analysis
Descriptive statistics of the study population will be completed. Univariate relationships between potentially relevant clinical and demographics factors will be determined.
T-test or Wilcox-Mann-Whitney test and chi-squared test will be used to determine differences and relationships between variables.
Assistance in statistical analysis has been sought from the center for Study Design and Biostatistics.

Cost, Compensation and Participant Reimbursement
During the initial pilot study, families will not bear the cost of acquiring a TENS unit and a unit will be loaned to them after they are randomized. The unit will be returned at the end of the study. There will be no participant compensation or reimbursement.

Safety and Clinical Monitoring

Families will be contact weekly to monitor for any adverse reactions as well as to assess adherence to treatment protocol. Contact will consist of a phone call from study personnel. If unable to make contact a voicemail with follow-up number will be left.

Provisions for Research Related Injury

Patients and families will be counseled on known potential adverse reactions (redness and skin irritation) and to discontinue use if these should occur. At this time, there are no provisions for research related injury.

Future Work

The goal of this pilot study is to assess recruitment and adherence feasibility as well as understand averages and variability in improvement. These data will be used to power and perform a larger, randomized control trial to assess efficacy of home-based, PTENS and compare this to traditional behavioral therapy. Our goal is not to have the PTENS indication updated to show that it can be used for voiding dysfunction

Abbreviations

BBD Bowel and bladder dysfunction
ICCS International Children's Continence Society
ICD-10 International Statistical Classification of Diseases and Related Health Problems – 10th Revision
LUTD Lower urinary tract dysfunction
PTENS Parasacral transcutaneous electrical nerve stimulation
REDCap Research Electronic Data Capture software
TENS Transcutaneous electrical nerve stimulation
UTI Urinary Tract Infection

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Name
DOB
MRN

Date:

48-Hour Weekend Voiding Diary
Day 1

Time	Fluid Intake (oz.)	Voided Volume (oz.)	Leaks (Y/N)?	Was leak associated with strong desire (Y/N)?	Pad/Pull-up change (Y/N)?	Sensation of urgency (Y/N)?

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Name
DOB
MRN

Date:

48 Hour Weekend Voiding Diary
Day 2

Time	Fluid Intake (oz.)	Voided Volume (oz.)	Leaks (Y/N)?	Was leak associated with strong desire (Y/N)?	Pad/Pull-up change (Y/N)?	Sensation of urgency (Y/N)?

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Name
DOB
MRN

Starting Date:

Nighttime Wetting Log (14 nights)

Night	**Wet (Yes or No)**
Sunday	
Monday	
Tuesday	
Wednesday	
Thursday	
Friday	
Saturday	
Sunday	
Monday	
Tuesday	
Wednesday	
Thursday	
Friday	
Saturday	

Name
DOB
MRN

Date:

Dysfunctional Voiding Scoring System

Over the last month	Almost never	Less than half the time	About half the time	Almost every time
I have had wet clothes or wet underwear during the day	0	1	2	3
When I wet myself, my underwear is soaked	0	1	2	3
I miss having a bowel movement every day	0	1	2	3
I have to push for my bowel movements to come out	0	1	2	3
I only go to the bathroom one or two times each day	0	1	2	3
I can hold onto my pee my crossing my legs, squatting or doing the “pee dance”	0	1	2	3
When I have to pee, I cannot wait	0	1	2	3
I have to push to pee	0	1	2	3
When I pee it hurts	0	1	2	3
Parents: Has your child experience something stressful like the example below?	No (0)		Yes (3)	
Total				

Stressors: New baby, new home, new school, school problems, abuse (sexual/physical), home problems (divorce/death), special events (birthday), accident/injury, others

Bowel and Bladder Retraining and Fitness

Colon Clean-out

<u>For all children</u>

Recommended to be done on a weekend

Senna (Ex-lax®) squares – 1 square for 6-12 year olds; 2 squares for those over 12
Polyethylene glycol (Miralax®) – 17 grams (one capful) in 8 ounce of water
Take both senna and polyethylene glycol every 12 hours for four doses.
(For example, Friday evening, Saturday morning, Saturday evening and Sunday morning)

Stool should be clear/watery at the end of the clean-out. If not, repeat the following weekend.

Bowel Health Maintenance

<u>For children with bowel dysfunction, such constipation or fecal soiling</u>

Polyethylene glycol

Take polyethylene glycol daily – one capful in 8 ounces of water once per day. Adjust dose to maintain a soft, semi-formed bowel movement. This may require every other day dosing, half capfuls or two capfuls

Toilet sitting

After each meal and after school for 5-10 minutes sit on a toilet and practice deep breathing and pelvic floor relaxation techniques

<u>For all children</u>

Dietary changes

Eat plenty of fiber and drink plenty of water (see Guide to Fiber and Fluid below)
Age plus five equals the number of grams of dietary fiber a child should eat per day
Limit dairy to three servings daily – two 8-oz glasses of milk and one cheese/yogurt

Foods and Drinks to Avoid

Some foods and drinks are known to make you pee more, because they bother your bladder or because they have things that make you pee. It doesn't mean you can't have them at all, but limiting them will help you stay dry
Spicy foods
Sugary drinks, including juice
Caffeine

Fluid Timing

No fluids within three hours of bedtime
For example, if you go to bed at 9pm you should try not to drink after 6pm
This may mean eating dinner earlier!
It is ok to drink a sip of water if you need to take medicine

Exercise
Exercise, play sports or play outside at least sixty minutes five times per week

Guide to Fiber and Fluid
High Fiber Foods

Whole grain bread	Bran flakes
Whole wheat pasta	Oatmeal
Apples, with skin	Black beans
Raspberries	Green peas
Pears, with skin	Artichokes

Drink Plenty of Water

6 years old	6 cups (48 oz.)
7 years old	7 cups (56 oz.)
≥8 years old	8 cups (64 oz.)

Bladder Retraining and Fitness
Scheduled voiding
Timed voiding you should pee every two hours while you are awake
You may need to set a watch alarm to help you remember in the beginning
We have a note for school to give to your teacher, if needed

Double voiding after you pee you should wait ten to fifteen minutes and try to pee again
This is especially important at night to keep you dry
For example, before you get ready for bed you should pee, then after your brush your teeth, wash your face, and change your clothes, right before you go to bed, you should pee again
You can also do this before long car trips or activities that tend to make you leak

Midnight voiding set an alarm and wake-up once at night to pee
This is for kids who are mostly wet at night

Pelvic floor relaxation
Be sure to do at least 3-5 relaxation breaths during each void
Deep breath in and blow out through an open mouth to a count of five
For younger children, it may help to use bubbles or a pinwheel
For girls, sit up straight with your feet on the floor (or a stool) and your knees wide apart
It may help to take one foot out of your pants and underwear

At 6 weeks

Name
DOB
MRN

Date:

48 Hour Weekend Voiding Diary
Day 1

Time	Fluid Intake (oz.)	Voided Volume (oz.)	Leaks (Y/N)?	Was leak associated with strong desire (Y/N)?	Pad/Pull-up change (Y/N)?	Sensation of urgency (Y/N)?

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Name
DOB
MRN

Date:

48 Hour Weekend Voiding Diary
Day 2

Time	Fluid Intake (oz.)	Voided Volume (oz.)	Leaks (Y/N)?	Was leak associated with strong desire (Y/N)?	Pad/Pull-up change (Y/N)?	Sensation of urgency (Y/N)?

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Name
DOB
MRN

Starting Date:

Nighttime Wetting Log (Any 7 consecutive nights)

Night	**Wet (Yes or No)**
Sunday	
Monday	
Tuesday	
Wednesday	
Thursday	
Friday	
Saturday	
Sunday	
Monday	
Tuesday	
Wednesday	
Thursday	
Friday	
Saturday	

Name
DOB
MRN

Date:

Dysfunctional Voiding Scoring System

Over the last month	Almost never	Less than half the time	About half the time	Almost every time
I have had wet clothes or wet underwear during the day	0	1	2	3
When I wet myself, my underwear is soaked	0	1	2	3
I miss having a bowel movement every day	0	1	2	3
I have to push for my bowel movements to come out	0	1	2	3
I only go to the bathroom one or two times each day	0	1	2	3
I can hold onto my pee my crossing my legs, squatting or doing the “pee dance”	0	1	2	3
When I have to pee, I cannot wait	0	1	2	3
I have to push to pee	0	1	2	3
When I pee it hurts	0	1	2	3
Parents: Has your child experience something stressful like the example below?	No (0)		Yes (3)	
Total				

Stressors: New baby, new home, new school, school problems, abuse (sexual/physical), home problems (divorce/death), special events (birthday), accident/injury, others

At 12 weeks

Name
DOB
MRN

Date:

48 Hour Weekend Voiding Diary
Day 1

Time	Fluid Intake (oz.)	Voided Volume (oz.)	Leaks (Y/N)?	Was leak associated with strong desire (Y/N)?	Pad/Pull-up change (Y/N)?	Sensation of urgency (Y/N)?

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Name
DOB
MRN

Date:

48 Hour Weekend Voiding Diary
Day 2

Time	Fluid Intake (oz.)	Voided Volume (oz.)	Leaks (Y/N)?	Was leak associated with strong desire (Y/N)?	Pad/Pull-up change (Y/N)?	Sensation of urgency (Y/N)?

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Name
DOB
MRN

Starting Date:

Nighttime Wetting Log (14 nights)

Night	**Wet (Yes or No)**
Sunday	
Monday	
Tuesday	
Wednesday	
Thursday	
Friday	
Saturday	
Sunday	
Monday	
Tuesday	
Wednesday	
Thursday	
Friday	
Saturday	

Name
DOB
MRN

Date:

Dysfunctional Voiding Scoring System

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I have had wet clothes or wet underwear during the day	0	1	2	3
When I wet myself, my underwear is soaked	0	1	2	3
I miss having a bowel movement every day	0	1	2	3
I have to push for my bowel movements to come out	0	1	2	3
I only go to the bathroom one or two times each day	0	1	2	3
I can hold onto my pee my crossing my legs, squatting or doing the “pee dance”	0	1	2	3
When I have to pee, I cannot wait	0	1	2	3
I have to push to pee	0	1	2	3
When I pee it hurts	0	1	2	3
Parents: Has your child experience something stressful like the example below?	No (0)		Yes (3)	
Total				

Stressors: New baby, new home, new school, school problems, abuse (sexual/physical), home problems (divorce/death), special events (birthday), accident/injury, others

Appendix 1

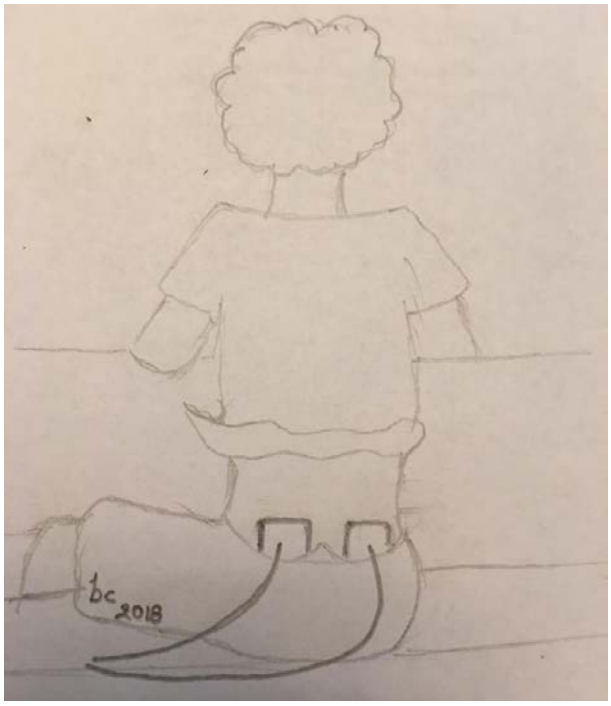
Controlling **O**veractive bladder and **P**ediatric **E**nuresis (COPE)

PTENS

What is PTENS?

Parasacral transcutaneous electrical nerve stimulation (PTENS) is electrical current that is used to stimulate the nerves near your sacrum. These are the nerves that stimulate your bowel and bladder. Transcutaneous electrical nerve stimulation was initially used for muscle pain and tension. Nerve stimulation has been shown in adults and children to improve symptoms of overactive bladder but traditionally needles are used to transmit electrical current. Use of transcutaneous electrodes for nerve stimulation for voiding dysfunction is thought to be safe and effective but, at this point, is investigational. It has not been approved for use by the Food and Drug Administration.

How do I use PTENS?



PTENS should be used three times per week for 30 minutes at a frequency of 10 Hz, a pulse width of 200 milliseconds. Electrode pads should be placed on the sacrum, on either side of the spine. These will be set by your nurse practitioner before you begin use. The intensity, or current, should be start at 10 milliamps and can be slowly increased in intensity to a maximum for 40 milliamps. These settings are on the dials number 1 – 8 on the top of your unit. You should NOT exceed 4. If there is pain, the settings should be turned down by 5 milliamps (half a setting) and re-tried until there is no pain. There may be a slight sensation. If there is visible muscle twitching, the settings should be turned down by 5 milliamps and retried until twitching stops. Treatments can be done sitting or lying down but should be done at a time when the child can be calm or relaxed. Pads should not be used if wet. Pads should not touch each other or the spine. A mild amount of redness after use is normal, but if there is pain or persistent redness, stop use and call your practitioner.

Where can I get a PTENS unit?

You can order a PTENS unit online from https://www.lgmedsupply.com/tenslg3000kit.html. They cost $40 - $50 depending on shipping and handling. You must bring your unit to your nurse practitioner appointment prior to use. You should NOT use the unit without first discussing use with your practitioner.

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