Optimal frequency used in transcutaneous electrical nerve stimulation (TENS) for treating nocturnal enuresis in children

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A. Study Background and Purpose

Nocturnal enuresis is a common pediatric problem of both urologic and neurologic/behavioral etiology. It can result in a great deal of patient and caretaker embarrassment and frustration with psychiatric consequences. While some patients respond to conventional therapy aimed at behavioral practices, many fails and need additional measures. The bedwetting alarm is usually next in line; however, many patients do not wear the device properly; "heavy sleepers" will usually not form the cognitive connections when the alarm sounds, and caretakers will not respond properly in awaking the patient during the alarm. After this comes pharmacologic therapy, which comes with its own set of medical side-effects and costs to the patient.

Neuromodulation has been shown to control various voiding disorders in both adults and children, along with experimentation with TENS units in controlling symptoms. TENS units placed in various locations stimulating a neurologic loop have been shown to control urinary symptoms in children with promising results [1,2,5,7,10,11,12]. TENS units have been shown to be safe with rare side effects and have the potential to be used in the convenience of a patient's home instead of undergoing surgery or multiple clinic sessions like other forms of neuromodulation.

Previous studies have shown evidence for neurologic manipulation in treating nocturnal enuresis [4,8,10]. If our study shows TENS units are an effective therapeutic option in decreasing nocturnal episodes, this form of management could be offered to the patient with the benefits of convenience of usage and avoidance of additional medications, thus enhancing the patient's and caretaker's quality of life that comes with the improvement of symptoms. Our recent findings have shown that when combined with proper behavioral voiding techniques, nightly posterior tibial nerve TENS for one month showed promising results in decreased enuresis and patient quality of life with lasting durability [18]. In that study, we used a pulse rate of 10 Hz during treatment, however this was chosen based on this frequency being used in prior studies. This study will identify the most efficacious pulse rate used when placing the TENS unit on the ankle to obtain the best results, which has yet to be determined. These findings will in turn lead to proper patient development, physical, mental, and overall health.

The goal of this study is to determine which pulse rate is the most effective to use in posterior tibial transcutaneous electric nerve stimulation for treating nocturnal enuresis in children.

Specific Aim: To determine if a short, moderate, or long pulse rate used in posterior tibial TENS (Groups 1-3) is optimal in improving nocturnal enuresis (decreased nocturnal episodes and increased patient/caretaker satisfaction).

Hypothesis: A moderate frequency used in TENS will show the most improvement in nocturnal enuresis compared to short and long frequencies.

B. Study Design

Children ages 5-18 years old referred to the pediatric urology clinic at Albany Medical Center Division of Urology and Northwell Heath Division of pediatric urology for primary nocturnal enuresis will be screened for enrollment. Information shared between these two institutions will be de-identified (i.e., age, gender, and randomization number will be shared, but name, date of birth, and medical record

number will not be shared). Behavioral modification (limiting evening drinking, double voiding prior to bedtime, bowel habits, social anxiety factors) will be utilized first. Patients who fail will next be offered therapy with a bedwetting alarm device or a TENS unit as an alternative, and those who chose TENS therapy will be included in the study. Patients who have previously tried pharmacologic treatment for nocturnal enuresis or alternative therapy for urologic disorders within the past 30 days, daytime incontinence symptoms, known "high volume" voiders (determined from history), bedwetting episodes on the average of less than one time per week, medications predisposing to incontinence (e.g., Lithium for bipolar disorder), other known voiding or neurologic disorders (e.g., overactive bladder, myelomeningocele), secondary etiologies for nocturnal enuresis (e.g., cystitis, obstructive sleep apnea, urinary fistulae), prior use of a TENS unit or other neuromodulation for bedwetting, and any contraindications to usage of a TENS unit such as having a pacemaker will be excluded. Patients who have previously tried the bedwetting alarm will not be excluded from the study.

The patients will be randomized into three groups of 30 patients each. Group 1 will be the long frequency set at 2 Hz. Group 2 will be the moderate frequency set at 10 Hz. Group 3 will be the short frequency set 150 Hz. There is no sham group in this study as we have previously found posterior tibial TENS to be effective and lasting, and as such all patients will be treated. We will aim to recruit 30 patients per group for a total of 90 patients.

Study Procedures

The first visit (Day 0) will take place in the clinic during the patient's routine visit. A detailed explanation of the purpose of the study, along with the risks and benefits of TENS will be given to the patient and parents by a provider prior to obtaining informed consent for enrollment into the study. After informed consent and assent, if applicable, has been obtained, parents or the patient will fill out the Pediatric Urinary Incontinence Questionnaire (PIN-Q), a validated tool for measuring quality of life in children with bladder dysfunction [6]. The patients and parents will be taught behavioral modification and the parents/patients of enrolled patients will fill out nightly voiding diaries, recording nighttime incontinence episodes and subjective "wet sheets" scale per night (dry, damp, wet, soaked) for 30 days prior to randomization into the treatment arms.

After the 30 days the patient will again be seen in the clinic for the randomization visit (Day 30). The PIN-Q will be completed, and the voiding diary collected. The diary will be reviewed for nocturnal enuresis episodes and the patient will be randomized into the study if they have at least 2 nocturnal enuresis episodes per week. If the patient does not qualify, they will be offered therapy with a bedwetting alarm device or other treatment.

The parent will receive the TENS unit and electrode pads for their child. The patients/parents will be instructed on how to use the device including positioning of electrodes, as well as given written instructions. The TENS unit settings will be pre-determined at the clinic and measures will be taken to ensure that the settings cannot be altered at home. The child's TENS unit will be set at a frequency determined by randomization, pulse width of 260 seconds, and an intensity to be determined in the office based upon when the child feels sensitive to the TENS unit. The child will be randomized and will place the electrodes along the posterior tibial nerve on the medial ankle each night before bed time for 15 minutes for a total of 30 days.

Group 1 he/she will be in the short frequency group. This means that the TENS therapy will use a pulse rate of 2 Hz.

Group 2, he/she will be in the moderate frequency group. This means that the TENS therapy will use a pulse rate of 10 Hz.

Group 3, he/she will be in the long frequency group. This means that the TENS therapy will use a pulse rate of 150 Hz.

Parents/patient will be given a voiding diary again for the month that they are using the TENS unit before bedtime. In this diary, the number of incontinent episodes, the severity of wetness each night, and the duration of TENS therapy, and adverse reactions to the TENS unit will need to be recorded.

At the end of the 30-day treatment period the visit will be done in the office (Day 60).
The TENS unit and the treatment voiding diary will be returned, and the PIN-Q will be completed. The parents/child will also be asked the question "Would you use TENS therapy again for your [child's] bedwetting problem?" Any persistent issues will be addressed during the final visit as well.

C. SUBJECT POPULATION (WHO, WHAT, WHERE)

Inclusion criteria for cases:

1. Age 5-18 years of age seen at Albany Medical Center Division of Urology
2. Presenting with nocturnal enuresis (more than 1x a week)
3. Failed Behavioral modification treatment (limiting evening drinking, double voiding prior to bedtime, bowel habits, social anxiety factors)
4. Ability to provide informed consent and assent and complete study requirements

Exclusion criteria for cases:

1. Patients who have previously tried pharmacologic treatment for nocturnal enuresis, neuromodulation or other alternative therapy for urologic disorders within the past 30 days
2. Daytime incontinence symptoms
3. Known "high volume" voiders (determined from history)
4. Bedwetting episodes on the average of less than two times per week,
5. Medications predisposing to incontinence (e.g., Lithium for bipolar disorder)
6. Other known voiding or neurologic disorders (e.g., overactive bladder, myelomeningocele, interstitial cystitis, etc.)
7. Secondary etiologies for nocturnal enuresis (e.g., cystitis, obstructive sleep apnea, urinary fistulae, heart disease)
8. Any contraindications to usage of a TENS unit (pacemaker or other implantable device, lymphedema, pregnancy, malignancy, bleeding or clotting disorders, unhealthy tissue, seizure disorders, impaired cognition)
9. Any history of heart disease or complications

D. DATA ANALYSIS

The data collection list is attached to the protocol. The data will be collected on a deidentified excel spreadsheet by patient study number and the deidentified data will be entered into the database.

The source documents and informed consents will be kept in the Urology Research Office.

The objective of this study is to evaluate which pulse rate is the most efficacious in transcutaneous electric nerve stimulation (TENS) as a therapeutic option for nocturnal enuresis in children. The proposed study will be a randomized clinical trial. There will be three treatment arms:

- 1. Group1:TENS pulse rate is set to 2 Hz
- 2. Group2:TENS pulse rate is set to 10 Hz
- 3. Group3:TENS pulse rate is set to 150 Hz

The study will be conducted for a total of 2 months (60 days), with two 30-day phases:

1. Baseline Measurement of" wet nights"(without treatment)for30days[Month1]
2. Active TENS treatment for 30 days [Month 2]

The Pediatric Incontinence Quality of Life Measure questionnaire (PinQ) is completed at the end of the baseline month. Patients who record 2 wet nights per week (a total of 8/30=27% wet nights) will be eligible for the TENS study. Those who record less than 2 wet nights per week will be ineligible for the TENS study but will be offered therapy using a bedwetting alarm device or other treatment.

RANDOMIZATION

Subjects will be randomly assigned with equal probability to either one of the three study groups. Randomization will be done by the statisticians at AMC to provide randomization. Allocation-concealment will be achieved by using sealed envelopes opened only after subjects are enrolled. Rrecord keeping will be from daily patient diaries before and during TENS treatment. The number of wet beds per month, the compliance rate (used TENS or not), the wetness scale (0 to 3), whether there was wetness during the day, whether there was a bowel movement, the PinQ scores before and at the completion of treatment, and any patient comments are recorded. Patient demographic will include age, gender, and pertinent urological history, if any.

BLINDING

There will be no blinding. Both study participants/caretakers and physicians will have knowledge of the treatment assignments.

INTENTION-TO-TREAT

All subjects will be analyzed according to the intention-to-treat [ITT] principle. A patient will be considered evaluable and will be included in the intention-to-treat analysis if the patient has documented at least 12 sessions of their designated TENS treatment (about 3 times a week of TENS therapy. Analyses that take into account the actual treatment received (e.g. non-compliance, etc.) will be carried out as a secondary analysis (per protocol [PP] analysis).

Primary Statistical Objective:

The primary objective of the study is to compare the three TENS treatment groups after one month of treatment, with respect to:

The reduction in the number of "wet nights" from baseline to after one month of therapy

The proportion of responders after one month of therapy

The change in PinQ scores from baseline to one month of therapy.

Secondary Statistical Objectives:

Secondary objectives include: comparison of the three treatment groups with respect to the number of "wet nights" and PinQ scores, separately, over time (by weekly diary entries)). Analysis will be carried out to determine if there are time dependent changes in the number of "wet nights" or in PinQ scores across the three TENS treatment groups. The number of "wet nights" according to severity will be examined as well. This will generate information on whether tolerance or sensitization occurs with this treatment.

Pairwise comparisons of TENS groups will also be carried out to compare each arm with one another using Tukey's multiple comparison tests.

Outcome Variables and Schedule of Assessments:

The primary outcome variable of interest is patient's percentage change in "wet nights" from before to during TENS. Also evaluated will be the response to treatment at the end of the 30-day TENS therapy period. A patient is said to have a (favorable) response to the treatment if he/she has a decrease of at least 50% in the number of "wet nights" in a month from baseline to after one month of TENS therapy.

Demographics and patient characteristics will be collected at baseline (age, gender, medical history). The following outcomes will be measured at baseline and at 1 month (at the end of the 30-day TENS therapy):

- Number of "wetnights"
- Severity of enuresis (dry, damp, wet, soaked)
- PinQ scores

Statistical Methods

For the primary objectives:

- Analysis of variance with a fixed effect of treatment with Tukey's multiple comparison test will be used to test for differences in the reduction in wet nights among the three treatment arms. Reduction will be parameterized as a relative change from baseline to one month. PinQ response before and after treatment will be compared among the three groups using repeated measures ANOVA with Tukey's multiple comparison tests.
- The Chi-square test or Fisher's exact test, as appropriate, will be used to compare the rates of response between the three treatment arms at the end of the 30-day treatment period.

For the secondary objectives, a repeated measures analysis of variance will be used to analyze the outcomes of interest on a week to week basis (number of "wet nights"). A treatment-by-time interaction will be examined to determine if the patterns of change in "wet nights" or PinQ scores over time differ across groups. Adjusted pairwise comparisons (Tukey or Bonferroni method) will be used to compare treatment groups to one another.

Data transformations may be applied, if necessary, in order to meet the required standard model assumptions.

Sample Size Considerations

We propose to recruit 30 patients to be randomly assigned to each of the three groups for a total of 90. Allowing for 20% dropout rate (due to non-compliance, insufficient number of treatment sessions, lost to follow-up or protocol violation, etc.), we expect 24 patients per group with complete evaluable data. The primary outcome variable will be percentage change in the number of wet nights relative to baseline. The study will have 81% power to detect differences in the change in percentage of wet nights among the three groups of 30% or more. This calculation also assumes that the normal month to month variation is percentage of wet nights is 30% and an alpha of 0.05.

Based on investigator expertise and some published studies, we assume that the proportions of responders based on our criteria of a "favorable response" for each of the three TENS groups will be 70% for moderate frequency (Group 2), 60% for short frequency (Group 1), and 40% for long frequency (Group 3).

The estimated 60% response rate for the sacral region stimulation was based on studies by Lordêlo1 et. al. (2010) and Oliveira2, et. al. (2013). Our previous findings showed placing the TENS unit on the foot was superior to the sacral region with frequencies set to 10 Hz, which is our moderate frequency in this study. We also believe that the response will be better with a lowfrequency compared to a high frequency.

Conduct of the study

The principal investigator, Dr. Adam Howe, is responsible for overall oversight of the data, monitoring the data, assuring protocol compliance, and conducting the safety reviews. Our prior study showed all patients enrolled in the study had no safety concerns. Dr. Howe will also be responsible for compiling the data sheets, day to day oversight of research and ensuring the integrity and privacy of the data. During the review process the principal investigator, along with the other investigators, will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment after 30 patients have been enrolled (half-way point of the study). The principal investigators or the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.

Any worsening symptoms or adverse reactions will be reported to the examiners, by way of voiding diaries, phone calls from parents, monthly clinic visits, or reported by parents aside from these instances. For patients with any severe or persistently worsening symptoms or adverse reactions, TENS therapy will be immediately discontinued, they will be removed from the study and considered treatment failures and receive medical treatment as necessary. Skin irritation is the most common adverse reaction to TENS units; however, this is mostly associated with allergy to the self-adhesive electrodes [9]. While pain may be a complication with TENS, studies have shown TENS is actually beneficial in treatment of pain over different areas of the body [14].

Patients with contraindications to TENS (eg, other electrical devices, pregnancy, bleeding or clotting disorders, unhealthy tissue, seizure disorders, malignancy, impaired cognition) will be excluded from the study. Patients will be taught safe practice with the use of a TENS unit, such as performing a sensory discrimination test in the office, checking and cleaning skin before starting a TENS session, monitoring skin for signs of irritation, changing adhesive on electrode pads after each use, securing

electrodes with even pressure distribution and full contact, and watching for signs of TENS unit malfunction requiring maintenance [9].

Patients and parents will be instructed to adjust the intensity to the level they can tolerate, so if the TENS intensity is too high then the patients will not be able to tolerate. Pain is the main issue with increased intensity (when it is not used to actually treat pain), therefore intensity will be minimized as per protocol to prevent this ("to the patient's tolerance"). Increased intensity would be assumed to lead to skin break down, however, reports of this are exceedingly rare (15). Patient education will be crucial here.

While reports of dermatitis have been reported in the literature, in most of these cases the dermatitis is caused by an allergy to the adhesive on the TENS electrode pads and not the actual electrical stimulation. Skin irritation can occur, but this is mostly seen in cases where TENS therapy has been used for multiple hours in a row. There has been only one case report in the literature (and not even searchable in Pubmed) of an actual burn from a TENS unit (16). In contrast, TENS therapy is actually used for pain relief on burn patients. Therefore, the risk of being burned from TENS therapy is extraordinarily low.

The effects of prolonged TENS usage have been studied in the literature before. Joennsson et al showed TENS therapy, with setting the same as in our proposal, for a mean duration of 566 minutes (range from 362-770 minutes) did not lead to any adverse reactions in 20 children with overactive bladder (17).

E. RISKS

The risks are minor and unanticipated. If there are any irritation to the TENS unit, the patient will be taken off of the study.

Adverse reactions to the TENS units: The parents and patient will be closely monitored and encouraged to call during the treatment period with any questions, concerns, or if the child is not experiencing any adverse reactions to TENS therapy. Risks can include pain, skin irritation, dermatitis, or burns. The most common reaction to the TENS unit is skin irritation related to an allergy to the self-adhesive electrodes.

Safe use of TENS units: The parents and patient will be educated to safely use the TENS unit, including monitoring for signs of irritation, changing adhesive on the electrode pads after each use and securing the electrodes appropriately and alternating the side of each electrode in terms of laterality (for example, place the electrode pads on the right foot on one day, then on the left foot on the next day, etc.). Failure to adhere to safety guidelines could result in an adverse reaction to TENS therapy and dismissal from the study.

Malfunction of the TENS units: The parents will be taught how to monitor the TENS unit they are given for signs of malfunction that will require immediate maintenance.

F. BENEFITS

Patients enrolled into this study will have failed first-line conventional behavioral modification. The patients may or may not have previously tried the bedwetting alarm device and failed. They would be

offered TENS therapy and thus enrollment into the study as an alternative to pharmacologic therapy for nocturnal enuresis (ie, desmopressin, imipramine, anticholinergics) after proper counseling of the risks and benefits by the provider and signing an informed consent. TENS units have been shown to be safe with very rare side effects reported in studies. Patients experiencing side effects or adverse reactions to TENS will terminate treatment and receive prompt medical attention. Follow up after treatment will determine if continuation of TENS therapy should resume as to avoid unnecessary treatment delay with other modalities.

G. CONFIDENTIALITY

All data will be kept in an excel database file on the secure AMC network with access restricted to the study personnel which is HIPPAA compliant to protect the confidentiality of patients. Consents will be taken in private locations to ensure privacy is not invaded. Data will be stored until at least 3 years after IRB closure or after Publication whichever is longer.

H. OPTIONS

Rather than participate in this study the subject can opt for standard assessment and care.

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