Transcutaneous Electrical Nerve Stimulation of the Foot: Results of a Novel At-home, Noninvasive Treatment for Nocturnal Enuresis in Children

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OBJECTIVE To evaluate the effect of a novel at-home approach to electrical foot stimulation of peripheral tibial nerve branches on the frequency of nocturnal enuresis episodes in children.

MATERIALS AND METHODS Children aged 5 to 18 having 2 or more bedwetting episodes per week for at least 3 consecutive months were eligible. The study was a total of 6 weeks. Participants completed a baseline nighttime voiding diary during the first 2 weeks. This was followed by 2 weeks of foot stimulation for 60 minutes each night. During the stimulation period, and the following 2 weeks poststimulation, participants completed the nighttime voiding diary.

RESULTS Twenty-two patients with a mean age of 11.4 years (range 7-16) completed the study. Overall, there was a significant reduction in mean total wet nights from 9.0 ± 4.0 to 6.8 ± 4.8 during the stimulation period ($P < .01$) and a sustained significant reduction to 7.2 ± 5.0 wet nights during the poststimulation period ($P = .02$). Sixteen patients (72.7%) showed improvement of at least 1 less wet night during stimulation, demonstrating a significant improvement from a mean of 7.9 ± 3.7 to 4.8 ± 3.5 wet nights during the 2-week stimulation ($P < .01$) and maintained an improved mean of 5.1 ± 4.0 wet nights during the poststimulation period ($P < .01$). There were no adverse events experienced by any child.

CONCLUSION Transcutaneous foot stimulation is a well-tolerated, noninvasive, at-home treatment that may reduce the number of wet nights in children with nocturnal enuresis. UROLOGY 101: 80–84, 2017. © 2016 Elsevier Inc.

Nocturnal enuresis (NE) is a common problem in the pediatric population, affecting up to 8% of children at 10 years of age.[1] NE can have a profound psychologic impact on a child's self-esteem and social interactions, as well as contribute to parental frustrations and anxiety.[2,3] Despite this, NE is generally considered a self-limiting process with a 15% resolution rate per year, and an overall decrease in prevalence from 20% to 1% from the ages of 5 to 16 years old.[4] Three major pathogenic mechanisms have been proposed, with potential overlap among them: nocturnal polyuria, detrusor overactivity, and increased arousal threshold.[5] Treatment options, therefore, are targeted at 1 or more of these mechanisms in an attempt to temporarily improve the frequency of wet nights while the majority of children outgrow the behavior over time.

The mainstays of initial therapy are behavior modification, limiting evening fluid intake, bedwetting alarms, waking up the child periodically to void, and pharmacotherapy.[6,7] Medications such as desmopressin and tricyclic antidepressants have been shown to improve the frequency of bedwetting by 10% to 65%; however, relapse rates are high once discontinued and side effect profiles can limit long-term compliance.[8-12]

Percutaneous tibial nerve stimulation (PTNS) achieved Food and Drug Administration approval for the treatment of overactive bladder in adults in 2000 and has been shown to provide improvement in urinary incontinence

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episodes comparable to pharmacotherapy without adverse side effects.[13-17] A recent study evaluated the use of PTNS on adolescents with NE and showed a statistically significant improvement in wet nights per week; however, PTNS required weekly office visits and invasive needle insertion, making its general application difficult.[18] Parasacral transcutaneous electrical nerve stimulation (TENS) has shown promising efficacy in the treatment of monosymptomatic NE; however, it also required in-office treatment by trained practitioners.[19]

Our department has previously described how TENS of somatic afferent nerves in the foot can inhibit reflex bladder activity and increase bladder capacity in animals and humans.[20,21] TENS allows for convenient at-home treatment using pad electrodes placed on the skin surface, without the need for insertion of percutaneous needles or weekly clinic visits. We evaluated foot stimulation in children with nocturnal enuresis, assessing primarily for treatment compliance and tolerability, and secondarily for improvements in frequency of wet nights both during and after treatment. We hypothesize that foot stimulation would be well tolerated with an ease of application at home and reduce the number of wet nights per week in children with NE.

MATERIALS AND METHODS

This prospective study was approved by the University of Pittsburgh Institutional Review Board and was conducted at the Children's Hospital of Pittsburgh. Children referred to the urology outpatient clinic for nocturnal enuresis, defined as bedwetting episodes at least twice per week over a period of 3 months or longer, were considered for enrollment. The study was limited to children aged 5 to 18 at the time of initial consultation with monosymptomatic NE, that is, without daytime overactive bladder or incontinence symptoms. Any child who had not achieved full toilet training was excluded. Children with a known neurological diagnosis, implantable medical device, or other medical comorbidity potentially associated with urinary dysfunction were also excluded. As this was a first of its kind pilot study, our enrollment aim was 25 participants based on a reasonable number to demonstrate a benefit as well as financial limitations of our approved grant through the Center for Medical Innovation at the University of Pittsburgh.

After consent to participate was obtained, children underwent an in-office demonstration of the commercially available TENS device (LGMedSupply, Cherry Hill, NJ), with an electrode pad placed across the plantar bridge and another more proximal over the medial edge of the foot inferior to the medial malleolus (Fig. 1). The child then underwent a 5-minute test stimulation to ensure tolerability. TENS device settings (5 Hz frequency and 0.2 ms pulse width) were based on our previous study,[19] with the only variable parameter being the stimulation current (0-100 mA) that was increased slowly to a maximal intensity comfortable to the child and produced observable involuntary great toe contractions. If after the 5-minute trial the child perceived he/she would be unable to perform stimulation at home due to discomfort or anxiety, he/she was excluded from the study.

The 6-week study consisted of 3 separate 2-week periods during which the child or parent would complete a daily nighttime voiding log indicating if each night was wet or dry. The first 2-week period served to collect the child's baseline nighttime voiding severity, as no stimulation took place during this time. During the second 2-week period of the study, children performed foot stimulation at home for 60 minutes every evening and the stimulation was completed no more than 1 hour prior to bedtime. No stimulation took place during the final 2 weeks of the study, which served as the poststimulation period.

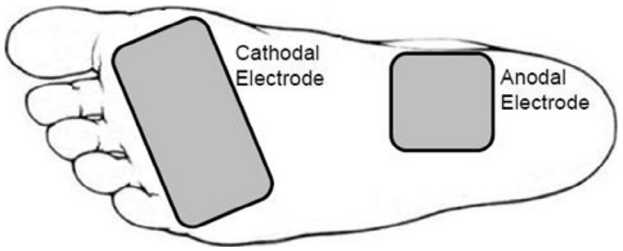

Figure 1. Placement of pad electrodes on the plantar surface (cathode) and medial heel (anode) of the foot to stimulate somatic afferent nerves in the foot.

Children and parents were asked to complete 2 validated questionnaires, including the Vancouver Nonneurogenic Lower Urinary Tract Dysfunction/Dysfunctional Elimination Syndrome (NLUTD/DES) questionnaire and the PedsQL 4.0 Generic Core Scales at the initial office visit, after the 2-week stimulation period and at the completion of the full 6 weeks of the study. The PedsQL 4.0 Generic Core Scales is a validated questionnaire developed by Varni et al to examine health-related quality of life in healthy children, and those with acute and chronic conditions.[22] The NLUTD/DES questionnaire is a valid, reliable tool consisting of 14 questions scored on a 5-point Likert scale to assess lower urinary tract and bowel dysfunction. Scores range from 0 (no complaint) to 4 (most severe). Question #7 specifically addresses NE. A total score of 52 is possible and scores of 11 or greater indicate bladder or bowel dysfunction, as demonstrated in initial studies.[23] At the conclusion of the 6-week study, all completed nighttime logs and questionnaires were returned along with the TENS units. Patients were compensated for completion of the study and return of all supplies.

Statistical analysis on nighttime voiding data as well PedsQL and NLUTD/DES questionnaire results was performed using *t* test or one-way analysis of variance to determine statistical significance ($P < .05$).

RESULTS

Twenty-five children were enrolled in this study, of which 22 children (12 boys and 10 girls) completed all 6 weekly nighttime logs and were included in our final analysis. Of these participants, 8 children had previously failed treatment with desmopressin alone, 1 had previously failed bedwetting alarm alone, and 5 had failed both desmopressin and bedwetting alarm. Two children had previously tried and failed a course of extended-release oxybutynin. No child was excluded for intolerability or anxiety after the initial trial in the office. One child was excluded due to receipt of incomplete nighttime logs, whereas another failed to return any completed nighttime logs and questionnaires. The mean age of all participants was 11.4 (range 7 to 16) years old. No subject was on any medication for NE at the

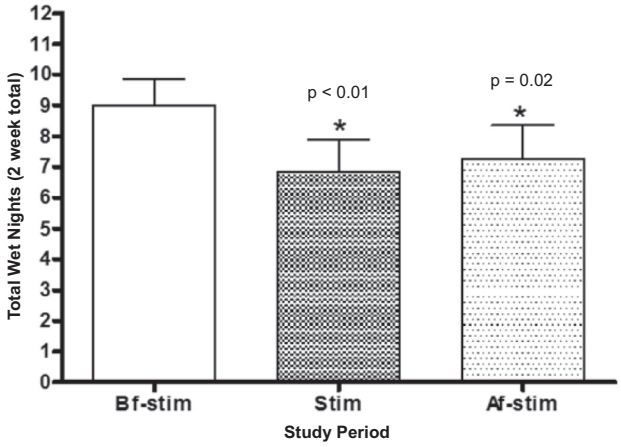

Figure 2. Results from all 22 participants on total number of wet nights per 2-week study period showing 2-week baseline wet nights (Bf-stim), wet nights during 2-week foot stimulation (Stim), and wet nights during poststimulation 2-week period (Af-stim). Asterisk indicates statistically significant difference from baseline by one-way analysis of variance.

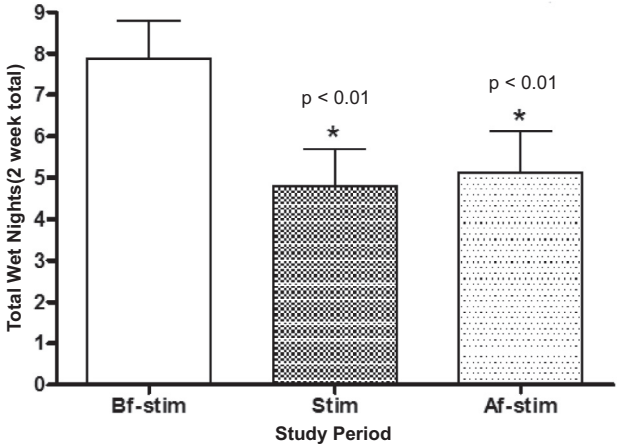

Figure 3. Results from 16 responders (patients that showed improvement of at least 1 wet night during stimulation) on total number of wet nights per 2-week study period showing 2-week baseline wet nights (Bf-stim), wet nights during 2-week foot stimulation (Stim), and wet nights during poststimulation 2-week period (Af-stim). Asterisk indicates statistically significant difference from baseline by one-way analysis of variance.

time of the study. During the 2-week stimulation period, the stimulation intensities used by the subjects were not significantly different between the first and second week: 19.5 ± 3.9 mA for the first week and 21.9 ± 7.5 mA for the second week.

During the first 2 weeks of the study, in which no foot stimulation was applied, the mean total wet nights for all participants was 9.0 ± 4.0. For the entire cohort, there was a significant decrease to 6.8 ± 4.8 wet nights during the 2-week foot stimulation period ($P < .01$) (Fig. 2). During the 2-week poststimulation period, there was a sustained improvement of 7.2 ± 5.0 wet nights ($P = .02$), indicating a prolonged residual effect as shown in Figure 2.

Of the 22 participants, 16 children (72.7%) had a clinical response with improvement of at least 1 wet night reduction during the 2-week stimulation period. The mean age of responders was 12.5 (range 8 to 16) years old compared to the mean age of nonresponders of 8.7 (range 7 to 10) years old, a difference which was statistically significant ($P < .01$). During the 2-week stimulation period, these 16 responders showed an improvement from a baseline of 7.9 ± 3.7 mean wet nights to 4.8 ± 3.5 mean wet nights ($P < .01$) (Fig. 3). Responders also showed a statistically significant improvement to 5.1 ± 4.0 mean wet nights ($P < .01$) during the 2-week poststimulation period as shown in Figure 3.

Table 1 shows the individual wet night response to stimulation and poststimulation for all 22 participants, categorized into responders (16 patients) and nonresponders (6 patients). In addition to age, there was a significant difference in the severity of baseline bedwetting between responders (7.8 wet nights) and nonresponders (12.0 wet nights) during the 2-week prestimulation period ($P = .03$).

There were no significant differences in the PedsQL questionnaire scores for both the child and parent between study periods, that is, prestimulation, stimulation, and poststimulation periods for either the total population or the responders alone. Whereas there was no significant difference between study periods in the NLUTD/DES questionnaire scores for the total population, there was a difference in the mean total NLUTD/DES score among responders: 13.9 prestimulation, 11.6 during stimulation ($P = .04$), and 10.5 during poststimulation period ($P = .04$). The individual question on the NLUTD/DES that provided this significant difference was question seven: "I wet my bed at night" (mean of 3.0 prestimulation to 1.9 during stimulation and 1.3 poststimulation, $P < .01$).

DISCUSSION

Given the vast prevalence of NE in the pediatric population, there remains a need for safer and more effective contemporary treatment options. Behavioral methods have shown some success as first-line therapy, but generally require a long training period before they are effective. The most popular example of this is alarm training, which can have up to a 66% rate of efficacy; however, compliance is often limited by its gradual onset of improvement, cumbersome equipment, and the disruption to sleep for the child, siblings, and parents.[6,7] Medications such as desmopressin and tricyclic antidepressants have been shown to improve the frequency of bedwetting episodes by up to 65%; however they have very high relapse rates of over 80% once discontinued.[8-11] Medications have potential side effects such as headaches, abdominal pain, emotional disturbances with desmopressin, and the more serious cardiac arrhythmias, hypotension, and hepatotoxicity with tricyclic antidepressants.[12] Our study indicates that transcutaneous foot stimulation may be an effective and safe

Table 1. Individual subject results from foot stimulation separated into responders (16 patients) and nonresponders (6 patients)

Patient Number	Age	Gender	Total Wet Nights (2-Week Period)		
			Before Stimulation	During Stimulation	After Stimulation
Responders					
3	15	F	13	2	1
4	9	M	12	7	5
5	9	F	6	1	3
6	12	M	4	1	0
7	9	F	4	1	1
8	13	F	4	2	1
9	12	M	7	4	5
11	16	M	6	3	4
12	8	M	6	4	4
13	13	M	10	8	8
15	15	F	9	7	8
18	10	M	8	7	6
19	15	M	4	3	4
20	16	F	5	4	5
21	16	F	14	11	14
22	10	M	14	12	13
Nonresponders					
1	9	F	13	13	13
2	9	M	14	14	14
10	9	M	14	14	14
14	10	F	13	13	14
16	7	M	13	13	14
17	8	F	5	5	9

treatment modality with a 72.7% response rate. In our total cohort, we showed an average improvement of 1 wet night per week and achieved 100% compliance without any adverse effects.

A recent study from Egypt using PTNS showed a 78.6% response rate of at least 1 wet night reduction per week in children with NE and significant improvements in multiple urodynamic parameters.[18] Their protocol, however, required weekly in-office treatments consisting of insertion of needle electrode at the child's ankle to directly stimulate the tibial nerve. De Oliveira et al described the use of parasacral transcutaneous nerve stimulation in this patient population and showed a 61.8% increase in dry nights over a 6-week period.[19] Although the results of these studies were promising, the need for weekly office visits and the invasive nature of the stimulation technique during PTNS severely limit the adaptation of these treatment modalities in the pediatric population. Our study has shown a comparable response rate through the transcutaneous stimulation of somatic afferent nerves in the foot, which does not require invasive needle insertion and can be performed conveniently in the comforts of a child's home by himself/herself or a parent. Transcutaneous electrical nerve stimulators and replacement pads are inexpensive and can be easily obtained through a variety of commercial outlets that we believe broadens the adaptation of this treatment modality without the need for children to see a specifically trained provider as PTNS requires.

Our data indicate that older children and teenagers with mild to moderate NE may be more likely to have a significant clinical response to foot stimulation than younger children with more severe symptoms. The average age of responders was 12.5 years old compared to 8.7 in nonresponders. The reason for this disparity may be related to the degree of bladder micturition inhibition and impact on overall bladder capacity in more mature bladders with a larger starting capacity. As our study did not include invasive urodynamic testing, this remains speculative.

Severity of symptoms may also be an important indicator for response. Five out of six of the nonresponders had 13 or 14 wet nights over the 2-week baseline period compared to only 3 out of the 16 responders with that severity of symptoms. Although 1 child (patient number 3) did show a dramatic improvement from 13 to 2 wet nights during stimulation, the great majority of children with this degree of NE were nonresponders. Patient number 3 was also one of the oldest participants at age 15 years old, whereas the 5 nonresponders with 13 or 14 wet nights were all age 10 or younger. This may indicate that age is actually a more significant driver of response than severity.

Prestimulation NLUTD/DES scores were only slightly above the threshold of 11 for dysfunctional elimination and this number decreased significantly in responders solely based on question #7 that specifically addresses nighttime wetting. Based upon the remainder of the questionnaire and in addition to our clinical history, these patients did not suffer from significant daytime voiding dysfunction, thus reducing the potential for confounding results.

The skin surface pad electrodes (Fig. 1) covered the skin areas innervated by medial and lateral plantar nerves and saphenous nerve. Therefore, it is assumed that the transcutaneous foot stimulation used in this study probably

activated somatic afferent fibers or terminals of these nerves. The medial and lateral plantar nerves are branches of the tibial nerve and it has been shown that percutaneous electrical stimulation of the tibial nerve with a needle electrode can prevent bedwetting in children or improve overactive bladder symptoms in adult.[13-18] Furthermore, the saphenous nerve is a branch of the femoral nerve and our previous study in cats has shown that electrical stimulation of the femoral cutaneous nerve can inhibit reflex bladder activity and significantly increase bladder capacity.[24] In addition, it is well known that tibial nerve stimulation can produce long-lasting poststimulation inhibition of bladder over-activity.[13-17] This may explain the 2-week long poststimulation effect observed in this study (Figs. 2, 3) if foot stimulation activated branches of the tibial nerve. Therefore, it seems reasonable to believe that foot stimulation improves bedwetting in children via stimulation of somatic afferents in the medial and lateral plantar nerves and/or saphenous nerve.

Limitations to this study include the small sample size and the lack of a placebo comparison group. We currently are enrolling patients in a randomized, placebo-controlled trial. The primary goal of this initial pilot study, however, was to determine tolerability and compliance using the device nightly for 2 weeks. Effectiveness was considered a secondary outcome in this initial phase of our study. The choice of 2 weeks of stimulation duration also reflects this, as our main goal was to assess the feasibility of at-home treatment and not optimal duration for maximal effect. Further study with longer stimulation duration is certainly warranted to explore this correlation and our ultimate goal would be to decrease the number of wet nights to zero; however, subjectively patients and parents were very pleased to even have 1 less night of bed wetting. We also acknowledge that patient compliance may decrease with a longer stimulation period. Although the nightly voiding log provides objective data, other measures such as bladder capacity were not obtained and future studies may require the use of urodynamics to fully assess bladder capacity. We feel that this initial study provides the basis for further investigation to determine the most optimal duration of stimulation, assessment of maintenance treatment for prolonged improvement, and direct comparison to other treatment modalities.

CONCLUSION

This study demonstrates that transcutaneous foot stimulation is a well-tolerated, safe, noninvasive, at-home treatment modality that may reduce the frequency of NE episodes in children. Further study is warranted to determine the optimal stimulation protocol to provide maximal and sustained benefits.

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