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Dorsal Genital Nerve Stimulation for the Treatment of Overactive Bladder Symptoms

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Abstract

Aim—To evaluate percutaneous placement of electrodes adjacent to the dorsal genital nerve (DGN) and measure the effects of electrical stimulation on symptoms of urge incontinence during 1 week of home use.

Methods—Prospective, multicenter study. Subjects with urge incontinence underwent percutaneous placement of an electrode using local anesthetic. Test stimulation was applied to confirm electrode placement and cystometry was conducted with and without application of electrical stimulation. A 7-day testing period with the electrode connected to an external pulse generator was performed and was followed by a 3-day post-treatment test period. Bladder diaries, 24 hr pad tests, and adverse event queries were obtained.

Results—Twenty-one women were enrolled with an average age of 52.7 years and average duration of incontinence of 6 years. Percutaneous electrode placement required 5–10 min and was well tolerated. There was no relationship between the acute effects of stimulation on cystometry and the results during home use. Pad weight was reduced by ≥50% in 13 of 17 subjects (76%) (4 did not complete 24 hr pad testing) and 47% of subjects reported ≥50% reduction in incontinence episodes. Of the subjects who reported severe urgency at baseline, 81% experienced a 50% or greater improvement. Seven subjects experienced nine adverse events ranging from skin irritation to pain and bruising around the electrode exit site.

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AUTHOR DISCLOSURES

Howard Goldman—Consultant: NDI Medical, Johnson & Johnson; Speaker honorarium: Pfizer, Novartis. Cindy Amundsen—Consultant: Medtronic; Fellowship, travel grants: Medtronic; Research grant: NDI Medical, Pfizer, Astellas, Allergan. Jeffrey Mangel—None. Julie Grill and Maria Bennett—Equity interests: NDI Medical; Director or employee: NDI Medical. Kenneth Gustafson—Owner: NDI Medical; Owner of patent(s): NDI Medical. Warren Grill—Equity interests: NDI Medical, Northstar Neuroscience; Consultant: NDI Medical; Research grant: Northstar Neuroscience.

Conclusions—Electrodes to stimulate the DGN can be placed percutaneously and a home testing period showed a reduction in overactive bladder symptoms with DGN stimulation.

Keywords

electric stimulation; overactive; urge; urinary bladder; urinary incontinence

INTRODUCTION

Electrical stimulation is an established treatment for refractory non-neurogenic overactive bladder symptoms. The Interstim® system (Medtronic, Minneapolis, MN), which applies stimulation to the sacral nerve roots, was approved by the FDA in 1997. However, sacral root stimulation is non-specific, which may contribute to its limited efficacy, and the location within the sacral foramina presents challenges to electrode placement and stability. The purpose of the present study was to investigate the feasibility of stimulating the dorsal genital component of the pudendal nerve (DGN) in persons with refractory non-neurogenic overactive bladder symptoms.

Stimulation of pudendal afferents has been shown to be effective in animal studies and in studies of neurogenic detrusor overactivity. The DGN carries sensory information from the glans of the penis or clitoris and forms a component of the pudendal nerve. Previous results in laboratory animals revealed prolonged suppression of the parasympathetic micturition reflex after stimulation of the DGN.[1] In persons with spinal cord injury and multiple sclerosis, DGN stimulation via a surface electrode inhibited bladder contractions and increased bladder capacity.[2–4] In addition, significant increases in the threshold volume for bladder contraction and the volume at the first desire to void were reported in persons with non-neurogenic urge incontinence using surface stimulation of the DGN, however, suppression of detrusor overactivity was not consistently seen.[5,6]

The mechanism of action of DGN stimulation to treat bladder overactivity is thought to be inhibition of the bladder by pudendal afferent stimulation.[7,8] Somatic inputs via the pudendal nerve reduce the output of the parasympathetic efferent innervation of the bladder by direct post-synaptic inhibition[9] and possibly by pre-synaptic inhibition of bladder afferents.[10] Somatic inputs increase the sympathetic outflow to the bladder (via the hypogastric n.) which inhibits the excitatory parasympathetic input to the bladder at the level of the vesical ganglia[11] and directly inhibits the smooth muscle of the bladder wall.

The primary purpose of this study was to determine whether electrodes could be properly placed and be effective and well tolerated by subjects during a 1-week home use testing period. Further, we sought to determine whether there were any acute effects of stimulation on cystometric parameters. This is the first study to evaluate the technique of percutaneous electrode placement next to the DGN in non-neurogenic urge incontinent patients.

MATERIALS AND METHODS

This was a prospective, multicenter study and institutional review board approval was obtained at the three institutions, The Cleveland Clinic, MetroHealth Medical Center, and Duke University Medical Center. Informed consent was obtained from all subjects prior to participation.

Subjects with a primary diagnosis of urge incontinence documented on a 3-day bladder diary were recruited. If subjects were on anticholinergics, they underwent a 5-day wash-out period. Baseline data included demographics, 24-hr pad test (the wet weight of all pads collected over a 24 hr period minus the dry weight of the same number of pads), and 3 day

bladder diary including: frequency, severity of urgency (none, mild, moderate, severe), pads per day (PPD), number of incontinent episodes (IE) per day, and the severity of the IE (Slight = a few drops, Moderate = 1–2 Tablespoons, Heavy = soaks pad/diaper or outer clothing). Exclusion criteria included spinal cord injury, multiple sclerosis, or diabetes with peripheral nerve involvement. Subjects were also excluded if they had significant stress incontinence based on history and bladder diary, a diagnosis of dry urgency/frequency, a current urinary tract infection or primary pelvic pain.

All subjects underwent percutaneous electrode placement using local anesthetic in the clinic procedure room. Published studies provide data on the safety and utility of the leads,[12] which had a coiled wire configuration and barbed tip that allows them flexibility without dislodgement. The electrodes were constructed from insulated stainless steel wire with a coil outer diameter of 580 μm. The anatomic course of the dorsal genital nerve (DGN) and the electrode implantation technique that enabled appropriate stimulation of the DGN were appreciated after a series of cadaveric studies by the authors. An 11 cm long 20G needle preloaded with the coiled fine wire was placed percutaneously in the midline of the mid-pubis and then advanced to between the crura of the clitoris and the pubic bone. Prior to withdrawal of the needle, test stimulation was applied to confirm proper placement, which was indicated by the subject reporting a sensation localized at the clitoris. If the sensation was not localized or the threshold was too high, then the needle was repositioned or advanced to achieve the desired response. After the proper placement of the electrode was confirmed, the needle was removed and the lead, which exited the skin, was attached to a cable for connection to the external pulse generator. The connector allowed the subject to unplug the cable for showering and dressing.

Subjects were asked to use their own words to describe the sensations produced by acute stimulation. For the final four subjects enrolled, words were categorized based upon previous subject reports and given to subjects to select the word the best described their sensation. To verify that subjects were accurately reporting when stimulation was *on*, four subjects across three sites were blinded to the administration of six trials of randomized stimulation and were asked whether they felt anything in the area of the clitoris during each trial. The presence of the pudendal (PA) anal reflex evoked by DGN stimulation was assessed either through visual observation of external anal sphincter contraction or surface EMG recordings from the EAS.

Cystometry was conducted with and without the application of electrical stimulation, and the volumes and pressures at which first urge to void, strong urge to void, and urgency were recorded. The subject was given a set of standard definitions describing the sensations of filling and asked to report these sensations.[13] The maximum fill volume or leakage volume was also recorded.

The subjects underwent a 7-day home test stimulation period as well as a 3-day post-stimulation period after the lead was removed. Bladder diaries, 24 hr pad tests, and adverse event queries were obtained during these periods.

“Improvement” was defined as a ≥50% reduction in each of the measured incontinence parameters, that is, 24 hr pad weights, IE/day, PPD, # of severe urgency episodes. Summary statistics were used to calculate the means, standard deviations, medians, and ranges of the subject data.

RESULTS

Twenty-one female subjects with urge incontinence were enrolled from 68 subjects screened across the three sites. The average age of the subjects enrolled was 52.7 (range 31–78) years.

Subjects presented with an average duration of incontinence of 6.3 ± 5.4 years. Fifty-two percent (11/21) of the subjects were Caucasian, 33% (7/21) were African American, and 14% (3/21) were Hispanic. The average body mass index of the subjects was 33.8 (range 19.2–47.1).

The lead placement procedure under local anesthesia was well tolerated by all subjects and the length of time to place the lead was 5–10 min. At the time of lead placement, the stimulus amplitude at which the subject first felt the stimulus (sensation threshold) was 4.3 ± 2.4 mA (range 2–10 mA), and the maximum amplitude that they could tolerate was 9.7 ± 4.7 mA (range 5–24 mA). The stimulus amplitude that subjects were sent home with for the week of stimulation was at the highest level that could be tolerated but did not cause discomfort (mean 9.6 ± 4.9 mA, range 4–24 mA). At the end of the week of stimulation the sensation threshold amplitude did not significantly change (5.6 ± 3.9 mA, 1–16 mA, $P = 0.06$ Wilcoxon signed rank test), but the average stimulus amplitude that subjects could tolerate increased to 19.0 ± 16.8 mA (5–60 mA range, $P = 0.001$ Wilcoxon signed rank test).

The PA reflex was observed in 10 of the 21 subjects tested, and there was no apparent relationship between the presence of the PA reflex and improvements in symptoms of incontinence during the 7-day testing period.

All subjects were able to report a sensation localized to the clitoris during delivery of test stimulation. The most common words that subjects used to describe the sensation were thumping (6), tingling (5), buzzing (4), and tapping, vibrating or pulsing (3). In the four subjects receiving random trials of stimulation *on* versus *off*, all were 100% accurate in reporting that they felt something when the stimulation was *on* and they did not feel anything when stimulation was *off*.

Cystometry with and without stimulation was completed in 20 of the 21 subjects enrolled in the study. One subject did not demonstrate urgency on the fill without stimulation, and thus testing was not repeated with stimulation. Of the 20 subjects who completed cystometry, 10 subjects demonstrated an increase in volume at first desire to void (mean increase = 35 cm^3), 16 subjects demonstrated an increase in volume at strong desire to void (mean increase = 48 cm^3), and 11 demonstrated an increase in maximum volume with stimulation (mean increase = 81 cm^3). Maximum volume represented either the leakage volume or the volume at which the subject could no longer tolerate filling. Logistic regression analyses conducted to evaluate each of these cystometric measures as possible predictors of each clinical measure indicated that none of the observed changes in cystometry, alone or in combination, were statistically significant predictors of any of the home use clinical outcomes.

Nineteen of the 21 subjects completed the week of stimulation. In two subjects the electrodes failed (one broke at the connection to the external cable and the second was dislodged by stretching of the lead wire), and these subjects did not complete the week of home stimulation. All 19 completed the bladder diaries recording voiding frequency, IE/day, severity of IE/day, severity of urgency, and PPD. Seventeen subjects completed a 24 hr pad test which was collected during the last day of stimulation treatment. One subject failed to collect pads and another subject's electrode was dislodged the last day of her stimulation week by stretching of the lead wire. In all three cases of electrode failure, the electrodes were removed from the body intact and no fragments were left behind.

Of the 19 subjects who completed the week of 'at home' stimulation, 15 (79%) subjects reported a reduction in their IE/day and 9/19 (47%) experienced a ≥50% reduction. Of those who improved by at least 50%, the mean reduction in IE/day was 89%. Fifteen (88%) of 17 subjects reporting on PPD had a reduction in PPD, with 8 of these subjects having ≥50% reduction. Of the 17 subjects who completed the 24 hr pad test, 15 (88%) had a reduction in

their pad weights. Among these subjects, 13 (76%) subjects had a ≥50% reduction in pad weight and eight (47%) were completely dry at the end of the week of stimulation (Table I). Of the 13 subjects who reported heavy leaks at baseline, 85% experienced at least a 50% reduction in heavy leaks with stimulation. Thirteen of 18 subjects (72%) had a reduction in urinary frequency. At baseline, 16/19 (84%) subjects reported severe urgency. Fourteen of these 16 subjects had a reduction in severe urgency events and 13 had at least a 50% reduction in the number of severe urgency events. Of those subjects with at least a 50% reduction in number of severe urgency events, subjects reported an average of 82% reduction in their severe urgency with stimulation.

At the end of the test stimulation week, subjects were asked to comment on how the stimulation affected their urge incontinence symptoms throughout the week. Common statements were that they were able to sleep longer at night (21%), that they had more time to make it to the bathroom/less urgency (26%), and if they did have an incontinence episode, the quantity was less (53%).

After stimulation was discontinued, some subjects reported that these benefits continued (Table II). Subjects were informally asked if the stimulation had any effect on their bowel or sexual function. Four (21%) subjects reported subjective improvement in their constipation. Only one subject had intercourse during the week and did not report any adverse effect.

Nine adverse events were reported in seven subjects across all centers (Table III). All adverse events were mild and were resolved at the time of the subject's discharge from the study (typically within 11 days of the implant procedure).

DISCUSSION

This study is the first to demonstrate the feasibility of DGN stimulation via a percutaneous electrode for the treatment of urge incontinence in the non-neurogenic population. Improvement in incontinence measures during the 1-week test stimulation period was documented in the majority of subjects. Most significantly, 76% of subjects had a ≥50% reduction in their pad weights and 47% of subjects were completely dry (no pads) at the end of the week of stimulation. Improvements were also observed in the number of heavy IEs, the average number of IEs, and severity of urgency events. Although this feasibility study did not employ a sham control, the 89% reduction in IE/day in the responder group is substantially higher than the 30–46% reductions in IE/day observed following placebo administration in studies of tolterodine (4 mg), solifenacin (10 mg), and trospium chloride (20 mg).

These findings are comparable to improvements seen with the sacral electrode stimulation technique.[14] In studies that were submitted for FDA approval of the Interstim® product, 47% of the overall subjects enrolled (including screened and implanted subjects) reported a >50% reduction in IE per day, 57% reported a >50% reduction in heavy leaks, and 52% reported >50% reduction in PPD.[15] Further, the present results obtained with percutaneous stimulation, are comparable to results of other innovative approaches using implanted hardware. Pudendal nerve stimulation produced reductions in number of IE, number of pads used, and leakage severity in two different series of patients with urge incontinence.[16,17] Stimulation with an electrode implanted periurethrally generated reductions in urinary frequency, leakage episodes, and urgency symptoms.[18]

This feasibility study confirmed that using a minimally invasive pre-pubic approach for percutaneous electrode placement was easily implemented by the physician, and the technique was easily transferred to other investigators. It also demonstrated that the electrode placement technique could to be performed under local anesthesia, without the

need for fluoroscopy, and was well tolerated by the subjects. The sensation from the stimulation was maintained and was also tolerable during the 1-week test stimulation period. The sensation thresholds did not change after the test stimulation week, which suggest that the electrode remained stable throughout the week of home use. However, subjects were able to tolerate higher amplitude stimulation after the test stimulation week, suggesting that they became acclimated to the stimulation sensation throughout the week.

We did not find a relationship between the effects of stimulation on cystometry and the effects of stimulation on incontinence symptoms during the home testing period. Use of cystometry to detect consistent and reliable acute responses so as to screen for potential candidates has been reported to be unsuccessful with other stimulation therapies in the non-neurogenic population. Several studies using sacral neuro-modulation reported no correlation between findings on cystometry during the acute stimulation period and clinical outcomes.[19,20] In a study involving five subjects undergoing pudendal nerve stimulation, statistically significant improvements were reported on cystometry outcomes as well as incontinence parameters after 6 months, however, the mean improvement in most incontinence parameters was less than 50%.[21] The increases in volumes on the second fill may have reflected accommodation rather than the acute effects of stimulation.[22]

The majority of subjects with reduced symptoms during stimulation also reported fewer IEs and lower pad weights 3 days after stimulation ended. This suggests a carry-over effect of DGN stimulation, as observed with other forms of neuromodulation.[23]

The results of this study suggest that DGN stimulation may reduce overactive bladder symptoms. Future studies with an implantable lead and generator will confirm if the results from sub acute testing is long lasting.

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TABLE I

Improvement in Incontinence Measures During 7-Day Stimulation Home Use Testing Compared to Baseline

	Subjects improved ≥50% (% improved)	Baseline mean	Post-Tx mean	% Change	95% confidence interval
Number of IE/day	9/19 (47%)	4.93 (n = 9)	0.56 (n = 9)	88.9%	24.5–68.8%
Number of PPD	8/17 (47%)	3.21 (n = 8)	0.72 (n = 8)	79.4%	25.3–72.2%
24 hr pad weight gram	13/17 (76%)	131.93 (n = 13)	19.52 (n = 13)	88.3%	53.5–92.0%
Number of Heavy IE/day	11/13 (85%)	1.39 (n = 11)	0.24 (n = 11)	86.7%	56.6–97.2%
Number of severe urgency	13/16 (81%)	2.36 (n = 13)	0.38 (n = 13)	82.4%	57.1–94.7%

Mean values at baseline and post-treatment are provided for responders (subjects improving by ≥50%).

TABLE II

Incontinence Measures Comparing Baseline to 3 Days Post-Treatment for Subjects Who Improved by ≥50% During Treatment

	Improved ≥50%		
	Baseline mean	**3 days post-Tx mean**	**% Change**
24 hr pad weight ml	131.93 (N = 13)	34.52 (N = 13)	69.8%
Number of IE/day events reported	4.93 (N = 9)	0.81 (N = 9)	83.7%

TABLE III

Summary of Adverse Events

Adverse event	Outcome	Subjects (of n = 21)
Skin irritation under surface electrode or tape/bandage	Topical antibiotic ointment used in one case and no action taken in other case. The events resolved at the time of discharge from the study	3
Redness/bruising around electrode exit site	No action taken and event was resolved at the time of discharge from the study	2
Bruising along pathway of external cable	No action taken and event was resolved at the time of discharge from the study	1
Pain/pressure w/stimulation	No action taken. Pain resolved	1
Pain (dull aching) at insertion site due to tape irritation	No action taken. Pain resolved upon removal of the electrode	1
Pain from surface stimulation due to electrode migration	No action taken. Pain resolved upon removal of the electrode	1