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Sacral Neuromodulation Effects on Periurethral Sensation and Urethral Sphincter Activity

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Abstract

Aims—To characterize the effect of sacral neuromodulation (SNM) on urethral neuromuscular function.

Methods—Following IRB approval, women with refractory overactive bladder (OAB) underwent standardized urethral testing prior to and after stage 1 SNM implantation. Periurethral sensation was measured using current perception thresholds (CPT). Striated urethral sphincter activity was quantified using concentric needle electromyography (CNE) and Multi-Motor Unit Action Potential (MUP) analysis software. Nonparametric analyses were used to characterize pre/post changes with intervention. Baseline CPT and CNE findings were compared between SNM responders and non-responders.

Results—27 women were enrolled in this pilot study with a mean age of 61±13 years. Twenty of 26 women (76.9%) responded to SNM and went to stage 2 permanent implantation. Four (14.8%) withdrew after stage 1 implantation; 3 of the 4 withdrawals had not had therapeutic responses to SNM. CPT and CNE parameters did not significantly differ from baseline 2 weeks after SNM. Pre-SNM urethral sensation was not significantly different between responders and non-responders. However, responders had larger amplitude, longer duration and more turns and phases at baseline approaching significance, reflecting more successful urethral reinnervation, than non-responders.

Conclusions—SNM does not alter urethral neuromuscular function two weeks post Stage 1 implantation. Women with more successful urethral reinnervation may be more responsive to SNM.

Keywords

overactive bladder; urethra; sacral neuromodulation

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Introduction

Overactive bladder (OAB) affects 33 million women in the United States with an estimated yearly cost of \$18.2 billion (1). Sacral neuromodulation (SNM) is an established treatment for patients with refractory idiopathic OAB (2). Four placebo-controlled studies of SNM in patients with refractory OAB showed improvements in patient symptoms ranging from 49-81% (3-5). The high cost of SNM has led to research efforts identifying predictors associated with a therapeutic response.

Predictors of response have been elusive because the mode of action of SNM in the treatment of OAB is unclear. Generally, SNM is thought to activate somatic afferent axons in the sacral spinal roots, directly inhibiting bladder pre-ganglionic neurons, and/or inhibit interneuron transmission in the afferent limb of the micturition reflex (6).

Urethral afferent and efferent neural dysfunction has been implicated in the pathophysiology of OAB. Urethral current perception threshold (CPT) testing quantifies the function of different populations of afferent nerves by applying sine wave stimuli at different frequencies (7-9). Numerous studies have demonstrated the neuro-selectivity of CPT testing and agreement between CPT and nerve conduction studies in several peripheral neuropathies (10-12). Kenton et al reported normative data for urethral current perception thresholds (CPT), and subsequently showed that women with OAB require more stimulation (higher urethral CPTs) to activate urethral afferent nerves (7). It has also been suggested that overactive bladder may be associated with loss of urethral sensation in women and a recent report studied the effect of one anticholinergic drug in restoring urethral sensitivity (13,14). The gold standard for quantifying efferent neuromuscular activity is concentric needle electrode (CNE) electromyography (EMG) (15). The association of urethral efferent neuromuscular activity and responsiveness to SNM is unknown.

It is plausible that SNM may be directly or indirectly affecting urethral innervation. In this pilot study, the primary aim was to determine the effect of SNM on urethral afferent nerve function using CPT testing and urethral efferent nerve function using CNE-EMG of the striated urethral sphincter muscle. We also sought to determine if baseline urethral CPT and EMG measures differed in women with refractory OAB and therapeutic versus non-therapeutic responses to SNM.

Materials and Methods

This is a pilot study of women with refractory idiopathic OAB planning to undergo testing for treatment with Interstim® therapy. Women who failed treatment with at least 2 anticholinergic medications and were planning to undergo placement of a sacral nerve modulator were approached for participation. Subjects were excluded if they had any of the following: neurologic disease, disease that might impair urethral tone or sensation, diathermy, QTc prolongation, cardiac arrhythmia, or other contraindication to SNM. This study was approved by the Institutional Review Boards at the University of Alabama at Birmingham and Loyola University, Maywood. All participants provided written informed consent.

At the initial visit, participants underwent a complete medical history, physical examination, urinalysis and urine pregnancy test in pre-menopausal women. All participants had urethral current perception threshold (CPT) testing and quantitative urethral concentric needle electromyography (CNE) before and after placement of the sacral nerve electrode (Interstim®, Medtronic, Minneapolis, MN).

Standardized CPT testing of the urethra was performed using a Neurometer® (Neurotron Inc, Baltimore, MD) as previously described (7). The Neurometer® is a constant current stimulator capable of delivering sine wave electrical stimuli at 3 frequencies, 2000 Hz, 250 Hz and 5 Hz, which selectively depolarize A- α , A- δ , and C fibers, respectively. CPT testing was performed with participants in the dorsal lithotomy position. Stimuli were applied via a Urotrode™ Midurethral Catheter Electrode (Neurotron Inc, Baltimore, MD) which is a 9 french catheter with an electrode 1cm proximal to a 3cc balloon.

After draining the bladder and inflating the catheter balloon, the balloon was gently positioned at the urethrovesical junction, so the electrode lay at the mid-urethra. The electrode was connected to the Neurometer®, and testing initiated at 2000 Hz. Stimulus intensity was gradually increased until first perceived by the participant, and then decreased until it was no longer perceptible. CPT values were obtained using a semi-automated forced choice paradigm where randomly chosen pairs of stimuli were presented as “A” or “B” with a brief rest period until a consistent perception threshold was reached. We repeated the process at 250 Hz and 5 Hz.

Anesthetic cream containing 2.5% lidocaine and 2.5% prilocaine (EMLA cream, Astra, Westborough, MA) was applied to the external urethral meatus 10 minutes prior to the CNE testing to optimize participant comfort. An Alpine Biomed Keypoint.NET electromyography instrument (Alpine Biomed Corporation, Skovlunde, Denmark) equipped with Multi-Motor Unit Action Potential (multi-MUP) software was used to process all raw EMG signals using standard filter settings (range, 5Hz to 10 KHz). An amplifier gain of 50 and sweep speed of 10ms per division was used. Quantitative electromyography (QEMG) was performed on all subjects. Multi-MUP analysis was utilized, which is thought to be the most sensitive QEMG technique for distinguishing neuropathic from control muscles (16,17).

A concentric needle electrode was placed in 3-4 insertion sites around the urethra. With the subject at rest then with slightly increasing pelvic floor muscle contraction, MUP activity was recorded using multi-MUP software at each insertion site. Quantitative MUP parameters, including amplitude, duration, number of phases and turns were recorded.

Sacral neuromodulation was performed in two-stages. Stage I consisted of placement of a quadripolar lead in the S3 foramen with confirmation of placement using fluoroscopy, patient sensation and visualization of bellows and plantar flexion of the great toe following standardized procedures. The electrode with the greatest response was set as the negative electrode. An adjacent electrode was set as the positive electrode. Amplitude was adjusted to the lowest effective level comfortable for the patient. Pulse width was set to 210 microseconds and rate was set to 14 MHz. Participants were reassessed at least one week after treatment for response to therapy. A positive response was defined as a subjective report of 50% improvement in symptoms of urgency urinary incontinence and/or urinary frequency by patient report and bladder diary. Participants also completed the urogenital distress inventory (UDI-6) and the incontinence impact questionnaire (IIQ-7) prior to and after implantation of the SNM device (18).

The primary outcome was difference in pre- and post-treatment urethral sensation as measured by CPT. Power and sample size calculations were based on a paired t-test detecting a 0.55 difference in scores (as previously observed at 250 Hz) (14). With 28 women we had 80% power to detect this difference. The paired t-test was used for normally distributed data. Otherwise differences in scores were analyzed with Wilcoxon signed rank test as done in similarly small studies (7,13,14). Tests of significance were two sided and evaluated at 0.05 level of significance. All statistical analyses were performed with SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

Twenty-seven women were enrolled in this pilot study. Demographic and clinical data are listed in Table I. Participants were predominantly post-menopausal and non-Hispanic Caucasians. Participants used a mean $\pm$ SD of 3.4 ± 1.1 prior anticholinergic medications for OAB treatment, and 9 (33.3%) continued their medication during the study period. One participant (4%) withdrew from the study prior to stage 1 implantation electing to not undergo SNM. Twenty of 26 women (76.9%) responded to SNM and proceeded to stage 2 permanent implantable pulse generator (IPG). Four (14.8%) withdrew after stage 1 implantation, 3 of whom did not have a therapeutic response to the SNM trial.

Baseline and post-SNM UDI-6 and UIQ-7 scores are listed in Table II for responders and non-responders. Responders experienced significant improvements in the UDI-6 and UIQ-7 (Table II; $p < 0.001$).

CPT and QEMG parameters did not significantly differ before and 2 weeks after SNM (Table III). Similarly, baseline urethral CPT values were not significantly different between responders and non-responders. However, baseline MUP analysis showed that responders had larger amplitude, longer duration and more turns and phases than non-responders, although this difference did not achieve significance (Table IV). Non-responders were significantly older than responders (median 75 years vs. 60 years; $p = 0.02$). Responders and non-responders did not differ with regard to BMI, current OAB medication use, or number of prior medications.

Discussion

Women with refractory OAB did not demonstrate measureable changes in afferent and efferent nerve function of the striated urethral sphincter muscle as measured by CPT and CNE, respectively. Women with baseline polyphasic MUPs, changes consistent with denervation – reinnervation injury, trended toward increased responsiveness to SNM therapy.

Evidence of the role of urethral sensation and neuromuscular function in overactive bladder is growing (8). Our finding of an elevated urethral CPT threshold in women with OAB is consistent with prior findings, but in this pilot study, we did not find a reduction in this threshold with SNM therapy (13). We recently demonstrated that solifenacin resulted in decreases in urethral sensation 4-6 weeks after initiating the medication suggesting that afferent or sensory changes may occur more quickly than efferent changes; however, we did not see this effect with SNM (19). If SNM promotes axonal regrowth, it may take longer than 2 weeks to demonstrate EMG evidence of reinnervation changes in the urethra. Our prior work did not include measures of efferent function.

Very little data exist on the effect of SNM on the urethra. Wyndaele et al described changes in urethral sensation in a series of 7 women receiving SNM for lower urinary tract symptoms (20). However, only one woman had overactive bladder and her baseline threshold was not provided. They reported that there were no differences in thresholds whether the device was on or off. We did not observe changes in urethral sensation after SNM in this series.

Women with refractory OAB who had a therapeutic response to stage I SNM trended toward having baseline polyphasic MUPs, which are changes consistent with denervation – reinnervation injury. When a motor unit is injured, peripheral sprouting from neighboring axons results in higher amplitude, longer duration MUPs. These data suggest that women in whom SNM is effective may start with better urethral innervation than those who do not

respond to this therapy. The finding of improved response with more successful reinnervation is consistent with the common understanding that SNM acts by stimulation of afferent axons in the spinal roots (6). Similarly, it is consistent with the ‘guarding’ reflex where urethral pressure increases with bladder filling and results in a negative feedback loop to inhibit spontaneous detrusor contractions (21). Our findings suggest that a successful response to SNM may be dependent upon intact motor units. Further study is needed to confirm this observation and hypothesis.

The trend toward better reinnervation as reflected by MUP analysis being predictive of response to SNM therapy is consistent with Groenendijk et al, who described the effect of urodynamic urethral instability in 19 women with OAB who underwent sacral nerve stimulation (22). They found that resolution of urethral instability was predictive of response to sacral nerve stimulation. The trend that we observed did not achieve statistical significance and may have been confounded by the age difference between responders and non-responders as well as our limited sample size in this pilot study.

The strengths of this study include the important research question with wide-ranging implications for treatment in a severely impacted population. Also, the prospective cohort design allowed for the investigation of multiple outcomes. Further, this is also the first study to report CNE EMG parameters for a cohort of well-characterized women with OAB. The study is limited by the failure to meet the targeted enrollment by one participant as well as greater than expected variability in the urethral sensation primary outcome. We also had 18.5% drop out from this small series. Therefore, this small pilot study is descriptive and hypothesis generating.

Conclusions

In this pilot study, sacral neuromodulation did not significantly alter urethral sensation or neuromuscular function. There may be an association of better urethral neuromuscular function and response to sacral neuromodulation, requiring larger trials with longer-term follow up. These findings support the growing evidence of the role of the urethra in overactive bladder and further studies are needed to further characterize and confirm this association.

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Table I

Demographics and Clinical Data

Demographic	Sample (n=27)
Age	61.3 ± 12.9
Race/ethnicity Non-Hispanic Caucasian African American	20 (74%) 7 (26%)
Body Mass Index	33 ± 9.6
Vaginal Deliveries (median, range)	2 (1-9)
Number of prior OAB medications	3.4 ± 1.1
Current OAB medication use	9 (33%)
Prior Hysterectomy	22 (81%)
Prior Surgery for Prolapse or Incontinence	14 (52%)
Diabetes	3 (11%)
Smoker	4 (15%)
Postmenopausal	24 (89%)
Vaginal Estrogen Use	9 (33%)

Table II

Baseline and Median Differences in Urinary Symptoms after Sacral Neuromodulation

	Baseline (n=27)	Median (IQR) Difference Responders (n=19 [*])	Median (IQR) difference non-responders (n=3)	P-value
UDI-6	59.1±24	40.1 (27.5, 52.7)	−4.2 (−31.5, 23.2)	<0.001
UIQ-7	64±28	44.4 (29.4, 59.3)	−3.2 (−62.7, 56.4)	<0.001

^{*} One responder had missing data for pre-SNM quality of life measures

Table III

Urethral Sensation and Urethral Sphincter Activity Pre- and Post-Sacral Neuromodulation

		Pre-SNM	Post-SNM	P-value
	N	Urethral Sensation – Current Perception Threshold		
CPT				
2000 Hz	21	377 (280, 561)	433 (269, 678)	0.58
250 Hz	21	183 (85, 267)	164 (111, 307)	0.91
5 Hz	19	47 (23, 87)	53 (16, 76)	0.93
		Urethral Sphincter Activity		
Amplitude (μ V)	20	115.5 (90.9, 164.5)	129.0 (98.0, 149.5)	0.76
Duration (msec)	20	5.8 (4.2, 7.4)	5.3 (3.8, 6.3)	0.13
Turns/Amplitude	20	0.30 (0.14, 0.63)	0.34 (0.22, 0.63)	0.76

Median (25th-75th IQR). Wilcoxon signed rank test.

Table IV

Baseline urethral sphincter activity for responders and non-responders to Sacral Neuromodulation

	SNM Responders (n=19)		SNM Non-Responders (n=4)		P-value
	Median (IQR)	Mean±SD	Median (IQR)	Mean±SD	
Amplitude (μV)	116.0 (78.9, 165)	142.9±78.0	92.4 (72.9, 114.1)	93.5±30.6	0.25
Duration (msec)	6.2 (4.1, 7.5)	6.5±3.5	4.4 (3.4, 5.3)	4.3±1.1	0.1
Turns (n)	0.8 (0.3, 1.4)	1.3±1.9	0.7 (0.3, 0.9)	0.6±0.5	0.5
Phases (n)	1.7 (1.5, 2.1)	2.0±1.3	1.5 (1.4, 1.9)	1.6±0.4	0.63
Turns/Amplitude	0.3 (0.2, 0.7)	0.5±0.6	0.4 (0.2, 0.7)	0.3±0.5	0.28

Median (25th-75th IQR). Wilcoxon rank sum test.