Sacral Nerve Stimulation: Neuromodulation for Voiding Dysfunction and Pain

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Summary: Voiding dysfunction, which includes incontinence, retention, and chronic pelvic pain, is a relatively frequent problem that can be difficult to manage. Neuromodulation via stimulation of the sacral nerves has been shown to improve these symptoms, although the exact mechanisms remain elusive. Techniques for nerve stimulation may vary, depending on the disease, location of pain, and the patient's anat-

omy. In addition to placement of electrodes on the sacral nerve roots, modulation has also been reported by peripheral branches of the sacral nerves including the pudendal and posterior tibial nerves. Newer surgical techniques have significantly decreased the morbidity of the procedures and increased the probability of a successful outcome. **Key Words:** Neuromodulation, incontinence, pelvic pain.

INTRODUCTION

Neuromodulation of the sacral nerves is an effective treatment for idiopathic urinary frequency, urgency, and urge incontinence. Its use for these prevalent conditions has become increasingly common and will be the primary focus of this review. The mechanisms for the efficacy of neuromodulation for voiding dysfunction are not completely understood, but this approach can substantially improve the quality of life for patients who are refractory to traditional pharmacologic therapy.¹ Neuromodulation of the sacral nerves has been used for treatment of chronic pelvic pain as well, but with less evidence for efficacy. Sacral nerve stimulation also has a role in treatment of chronic pelvic pain in which spinal cord stimulation may not be effective.²

The use of neuromodulation to enhance spontaneous voiding function in patients who are generally neurologically intact is in contrast to the role of direct stimulation of the anterior nerve roots to induce bladder contraction in patients with paraplegia and retention. In this latter procedure, the sensory nerve roots are also transected, to reduce sphincter dyssynergia. Stimulation has a role in assisting bladder emptying as well.³

The history of stimulation of pelvic nerves in regards

to lower urinary tract function dates from at least the 1860s, with studies of stimulation of the spinal cord of dogs leading to observation of the importance of hypogastric and pelvic nerves for bladder function contraction. Subsequently, there was a report of a clinical application using intravesical electrical stimulation for urinary retention.⁴

Brindley³ developed an electrode model in which stimulation of ventral roots of the bladder and sphincter could be activated. Stimulation of pelvic nerves directly was noted to have inadequate chronic responses.⁴ Fandel and Tanagho cite Schmidt's contributions in the 1980s in developing a staged approach to neuromodulation: first, use of a test stimulation needle; second, placement of a temporary lead; and finally, subsequent permanent neuroprosthesis if >50% improvement of symptoms was noted.⁴ More recent multicenter studies provided data on neuromodulation that led to U.S. Food and Drug Administration (FDA) approval of sacral nerve root stimulation for clinical use for voiding dysfunction.^{5,6}

POSSIBLE MECHANISMS OF ACTION OF NEUROMODULATION FOR VOIDING DYSFUNCTION

Direct spinal cord stimulation is a well-established method for treatment of neuropathic pain. Its mechanism of action is generally assumed to be based on the gate-control theory of Melzack and Wall.^{7,8} Sacral nerve stim-

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ulation for control of pain is also thought to work by similar mechanisms. Possible mechanisms by which neuromodulation may affect lower urinary tract function include alteration of afferent and efferent feedback mechanisms at both spinal and supraspinal levels.^{9,10} This is not surprising considering the complexity of neurological control of voiding.¹¹

Voiding function is an integrated function requiring input from the parasympathetic system via the pelvic nerve, the sympathetic system via the hypogastric nerve, and the somatic system via the pudendal nerve innervating the rhabdosphincter. Voluntary control of voiding function depends on the interaction of the cortex and the pontine micturition center, which in turn modulates sacral cord voiding reflexes. These reflexes include suppression of bladder contractions associated with tonic sphincter muscle activity during filling phase and coordination of bladder contractions and relaxation of the sphincter during the voiding phase.

Bladder afferents consist of myelinated A delta fibers and unmyelinated C fibers. The A delta fibers are thought to be the primary mode of transmission for stimulation of stretch receptors in the bladder. Unmyelinated C fibers within the bladder are generally felt to be silent during normal bladder cycling, but may be activated with a variety of noxious stimuli and subsequently associated with facilitation of voiding.¹² In some diseases, such as multiple sclerosis and spinal cord injury, it is thought that some of the detrusor hyperactivity is related to abnormal increased activity of bladder C fibers, which thus present a potential therapeutic target. During the filling phase which accounts for the majority of the voiding cycle, the contractility of the detrusor is in an "off" position under primarily chronic inhibitory impulses to the sacral cord via the cortex mediated through the pontine micturition center.¹²

A number of reflex pathways may be potentially affected by neuromodulation. In the vesicosympathetic reflex, bladder filling may stimulate lumbar sympathetic activity, allowing greater accommodation of filling. The guarding reflex, in which increased sphincter tone is occurs with bladder fullness, is another feedback loop affecting continence. It is mediated both by sympathetic efferent pathways to the bladder neck and by activation of the external sphincter via the pudendal nerve.

Once voiding is initiated, there are positive feedback loops to optimize complete emptying of the bladder.¹² These include connections between the bladder afferent nerves with interneurons within the sacral spinal cord. The interneurons synapse with bladder preganglionic efferent parasympathetic neurons as a bladder-bladder reflex, as well as with neurons innervating the urethra to promote relaxation of the sphincter during voiding. Disease may disrupt the homeostasis of this complex process, leading to difficulty with either storage or emptying. Difficulties with storage may be urge incontinence,

caused by detrusor overactivity, or stress incontinence, caused by sphincter underactivity. Difficulties with emptying (leading to retention) or difficulties with holding are associated with sphincter overactivity or detrusor underactivity.

Spinal cord stimulation experiments indicate that the sacral cord location for detrusor activation is more limited in a vertical extent than the sphincter, although separate in location at the same horizontal plane.^{11,12} This has implications for attempting to separate bladder and sphincter functions in regards to spinal cord or sacral nerve root stimulation. Although testing for adequate location of the electrode during implantation uses current amplitudes to visualize contraction of muscles innervated by S3, therapy is generally performed at chronic amplitudes that are less than the activation threshold of somatic muscle.¹⁰ This suggests that beneficial effects are likely related to modulation of micturition feedback loops by afferent stimulation.

The mechanism of action of sacral neuromodulation is uncertain; it appears to affect both spinal and cortical centers of voiding control.^{9,10} Several rodent studies, using chemical cystitis and spinal cord injury models, suggest that changes in spinal signal processing are important. Stimulation inhibits the frequency of bladder contractions in both control and chemical cystitis animals, with a more pronounced effect in the animals with cystitis.¹³

When neuromodulation was combined with treatment with neurotransmitter antagonists, it appeared that non-NMDA (*N*-methyl-D-aspartate) receptors but not NMDA receptors were implicated in the effects of sacral neuromodulation. These studies also suggested a role for nitric oxide signaling in bladder hypersensitivity.¹⁴ In rodents, vanilloid receptor 1 (VR1) expression was upregulated in the dorsal horn of the spinal cord after spinal cord injury, and neuromodulation was also associated with reduced expression of VR1.¹⁵ Using a chemical cystitis model of HCl and acetic acid, the same group reported that although sacral stimulation (S1) could reduce voiding frequency rates, there did not appear to be a difference in the number of *c-fos*-positive neurons in the L6 spinal cord.¹⁶ However, because most patients undergoing implantation do not have spinal cord injury nor evidence of acute bladder inflammation, it is unclear whether the mechanisms described in these animal studies may be involved.

Human studies regarding possible mechanisms of sacral neuromodulation have used a variety of measurements, including urodynamic testing, somatosensory evoked potentials (SEPs), positron emission tomography (PET), electroencephalography (EEG), sensory threshold testing, and urinary biomarkers. Urodynamic testing in patients with idiopathic bladder overactivity indicates inhibition of detrusor overactivity without effect on urethral resistance or

strength of detrusor contractions during voiding.¹⁷ In contrast, in patients with nonobstructive retention with elevated urethral closure pressures, successful neurostimulation did not directly relax sphincter activity but rather the bladder was noted to have increased contractility.¹⁸

A number of studies have suggested supraspinal afferent pathways as a mechanism of sacral neuromodulation. Measurement of SEPs of the pudendal nerve found that sacral neuromodulation was associated with a significant decrease in pudendal SEP latency.¹⁹ EEG monitoring during cycling of a neurostimulator device demonstrated a cortical potential complex regardless of any conscious awareness of whether the device was activated. It was concluded the findings were compatible with modulation being active in the sensory cortex areas.²⁰ PET scanning has also contributed to the possible mechanisms of neuromodulation. In healthy controls, bladder filling was noted to increase activity in the midbrain and limbic cortical regions. In contrast, patients with idiopathic retention lacked brainstem activation with filling. Neurostimulation in the patients with retention was found to restore a more normal pattern of brainstem and cortical interaction in response to bladder filling.²¹ In a study using PET scanning of urge-incontinent patients, both acute and chronic effects were noted. Patients with neuromodulation chronically (>6 months) were noted to have decreased regional blood flow in the cingulate gyrus, ventromedial orbitofrontal cortex, midbrain, and midline thalamus, with increases to the dorsolateral prefrontal cortex. Patients who were scanned immediately after activation of the device were noted to differ from those with chronic stimulation (>6 months) in the associative sensory cortex, premotor cortex, and the cerebellum; this suggests a learning phase acutely.²²

Sensory thresholds for the bladder, urethra, and arm have also been measured in patients undergoing S3 neuromodulation. It was reported that the neuromodulation reduced the bladder but not the urethral sensory thresholds and that the effect did not seem to directly correlate with a positive clinical effect of the stimulation.²³ Such findings are consistent with altering of afferent pathways, although there are likely efferent feedback loops of neuroplasticity involved as well. Chai et al.²⁴ reported that, in patients with interstitial cystitis, neuromodulation not only improved voiding frequency and pain level, but also improved the pattern of urinary heparin binding epidermal growth factor and antiproliferative factor—two molecules that may regulate health of the turnover of the urothelium—toward normal levels.

SURGICAL TECHNIQUES

A number of technical advances developed over the last 10 years allow transforaminal sacral nerve modulation to be performed with minimal morbidity. The technique

for treatment of voiding dysfunction was originally developed by Schmidt, Tanagho, and colleagues,^{25,26} using an initial percutaneous placement of a single electrode lead through the sacral foramen. The lead was taped to the skin surface, but did not have any fixation at deeper levels. The lack of fixation allowed movement of the lead away from the area of stimulation and thus limited the length of a trial of neuromodulation. In patients who achieved a positive trial of neuromodulation, the subsequent surgical implantation of the permanent electrode was associated with moderate morbidity. This entailed an incision that was carried down to the level of the periosteum of the sacrum, to which a plastic anchor was affixed to hold the electrode in place. The cable connections to the generator were then tunneled using several incisions to the location of a pocket on the lower anterior abdominal wall.

Occasionally, patients who had an apparent positive benefit from neuromodulation with the transient temporary percutaneous lead did not improve as expected once a permanent electrode was implanted. One attempt to improve outcome was to perform a sacral laminectomy and attach bipolar electrodes directly to the sacral nerve roots bilaterally.²⁷ The trend, however, has been evolution of less invasive placement of electrodes. It was also noted in the earlier studies that placement of the generator on the anterior abdominal wall was associated with discomfort at the generator site, as well as prolongation of the surgical procedure. Currently, the generator in most cases is implanted in the subcutaneous tissue in the buttock region, which has been found to be acceptable and simplify the operative procedure.²⁸

Subsequent modifications to the technique included use of needles, wires, and dilators to place the electrode within the foramen next to the nerve root without the need to incise overlying muscle and fascia. Initially this was performed using an anchor system to the lumbodorsal fascia.^{29,30} Subsequently, a lead with plastic tines was developed, which fixes the electrode in place without the need for additional anchoring³¹ (FIG. 1 and FIG. 2). With this technique, the incision for insertion of the electrode is a centimeter or less under local anesthesia and also, importantly, allows the same electrode to be used for both test and chronic stimulation, thus diminishing the likelihood of a patient failing to respond once an internal generator is implanted. Peters et al.³² reported that the probability of test to implant rate improved from 52% to 94% and, when sensory response could be obtained during the implant, the reoperation rate declined dramatically.

One consequence of changing from a percutaneous lead taped to the skin to doing the test phase with a potentially permanent electrode fixed with tined leads is the ability to extend the trial of the test phase. Kessler et al.³³ found that this increased the number of patients exhibiting a positive

FIG. 1. Lateral x-ray view shows the InterStim (Medtronic, Minneapolis, MN) sacral nerve generator and lead, with four electrodes and plastic tines that anchor the lead for ease of percutaneous placement under local anesthesia.

response, allowing generator implant to increase from ~50% to ~80% when the length of evaluation was extended from a period of 4–7 days to at least 2 weeks. Another report, also from Europe, also indicated that ~75% of patients undergoing a staged procedure did have a positive test, allowing implantation of a pulse generator, when the screening was performed for an average of 30 days.³⁴

A number of reports have also been published regarding possible factors that could have predictive value. During implantation of the percutaneous electrode, both motor response and sensory response are obtained to determine S3 nerve root stimulation (FIG. 2). A positive motor response during the initial test phase tended to be more predictive, with a positive test defined as >50% improvement in symptoms. If only sensory response was elicited, just 4.7% of patients had a positive test, whereas 95% of patients with a successful test had a positive motor response.³⁵ Age >55 years has been reported to reduce the chances of success by ~30%, and more than three chronic comorbid conditions or neurologic disease also diminishes the odds of a successful response to neuromodulation.³⁶

The technique of percutaneous placement of a lead directly into the sacral nerve root foramen has the limitation of stimulating a single nerve root. Although this has generally been satisfactory for treatment of voiding dysfunction, and has improved some aspects of pain in patients with interstitial cystitis, treatment of neuropathic pain may benefit from the more extensive field of neuromodulation available with additional electrodes. Often, bilateral leads are placed percutaneously in a retrograde manner via the epidural space at a lumbar level.^{2,37} Haque and Winfree² described a variety of techniques, including transforaminal,

intraspinous, extraforaminal, and transspinal approaches. A percutaneous retrograde approach can be compromised by epidural fibrosis, stenosis, and spondylolisthesis.⁸

More invasive techniques have been described for treatment of spinal cord injury patients, in which stimulation of the anterior roots is combined with posterior rhizotomy³⁸ for treatment of chronic retention and incontinence. This approach to electrical stimulation to alter voiding function differs greatly from the more common neuromodulation used for treatment of frequency, urgency, and incontinence. In this approach, the stimulation is applied only intermittently (on demand), and at high intensity, to directly induce contractions emptying the bladder as opposed to more common continuous electrical massage of neuromodulation, which likely influences the complex spinal and cortical signaling pathways for treatment of idiopathic or non-neurogenic voiding dysfunction.

OUTCOMES FOR THERAPY

Voiding dysfunction

A multicenter trial evaluating neuromodulation of the sacral nerve roots for urinary urgency and frequency reported 51 patients from 12 centers implanted after a successful percutaneous trial phase.⁶ Those in the

FIG. 2. Posteroanterior x-ray view of sacrum after implantation of test leads. During the procedure, both motor (bellows and great toe responses) and sensory responses (stimulation felt in the scrotum, vagina or perineum) are used to confirm stimulation of the S3 nerve root.

control group had delayed implant of the device after 6 months of observation during which there was no significant improvement in parameters. Patients were followed at 1, 3, and 6 months and then at 6-month intervals. Urinary frequency, voided volume, and degree of urgency were all significantly improved. The number of daily voids declined by almost 50%, and correspondingly the volume of each void nearly doubled. Quality of life was also improved, as measured by the SF-36 instrument (e.g., <http://www.sf-36.org/>). After 6 months, the generators were turned off in the stimulation group and urinary symptoms returned to baseline. Once stimulation was again restarted, these patients regained sustained efficacy at 12- and 24-month intervals.⁶

Spinelli et al.³⁹ reported on a total of 196 patients enrolled in the Italian Register who had been implanted for a variety of voiding dysfunction. For patients with incontinence associated with detrusor instability, the mean incontinent episodes declined from about five a day to one; in patients with idiopathic retention the residual volume declined from 277 to 108 mL, with 50% of patients no longer needing catheterization.

The technique has also been shown to be beneficial in patients with nonobstructive voiding. In one center, 38 patients presenting with urinary retention were evaluated. Of these, 34 were found to have abnormalities of the striated urethral sphincter on electromyography consistent with the disorder known as Fowler's syndrome. The success of neuromodulation in this group, which is often refractory to other treatment,⁴⁰ was reported to be 68%.⁴¹ Another investigation found a successful outcome in 22 of 28 patients with retention (78%).⁴² Urodynamic studies confirm beneficial results treating patients with idiopathic retention, with postvoid residuals becoming minimal and uroflometry and pressure flow studies returning to near normal values.⁴³

Durability of neuromodulation effects is still in question. Most published studies, including those for FDA approval, are of relatively short duration (<1–2 years). Latini et al.⁴⁴ reported that 90% of patients maintained a 50% reduction of urge incontinence symptoms (median follow-up, ~1 year), and Siegel's group⁴⁵ reported that ~70% of their patients indicated an improvement of >50% (mean follow-up, 22 months). In women with retention due to Fowler's syndrome, nearly 80% of patients implanted were reported to have persistent benefit,⁴⁶ although 54% had required revision procedures. Some studies, however, have suggested a decline of effectiveness over time. A report from one site with up to 13 years of follow-up indicated that only 45% of the patients implanted for urgency and frequency had persistent improvement,⁴⁷ and Hohenfellner et al.⁴⁸ reported that nearly all patients with a history of neurogenic bladder dysfunction failed to have long-term durable benefit from implantation.

Anterior nerve root stimulation in paraplegic patients

to treat retention and incontinence is a relatively uncommon and invasive procedure, in which a posterior rhizotomy is commonly done at the same time, but beneficial results have been reported. In a study of 50 patients followed for 5–11 years, 41 continued to use the implant and 37 were generally continent; some benefit in regards to bowel and sexual function was noted, as well.^{49,50}

Pain

The device currently marketed for transforaminal sacral nerve root stimulation to treat voiding dysfunction (InterStim; Medtronic, Minneapolis, MN) is not specifically indicated for treatment of pelvic pain. Although Hohenfellner et al.⁵¹ reported that pain is less likely to respond to sacral nerve root modulation, a number of publications attest to the ability of such stimulation to relieve pain, as well as relieving voiding symptoms in pelvic pain patients treated for coincident voiding dysfunction.

In patients with interstitial cystitis, pain or discomfort is generally associated with increased urinary frequency and urgency. In this group of patients, improvements in pain were reported in a subacute study.⁵² Maher et al.⁵³ treated 15 patients with interstitial cystitis refractory to other therapy with sacral neuromodulation and reported a significant reduction of pain scores, from 8.9 to 2.4, in addition to improvements in voiding symptoms and quality of life parameters.

Siegel et al.⁵⁴ also reported a 60% significant improvement in pelvic pain in 10 patients at a median follow-up of 19 months. Everaert et al.⁵⁵ also treated a series of chronic pelvic pain and reported that success was inversely related to neuropathic pain, but that the 11 patients who responded appeared to have a durable response to ~3 years. A subsequent series of 21 implanted patients with interstitial cystitis, reported by Peters and Konstant, ⁵⁶ were followed for a mean of 15 months. Moderate to marked improvement in pain was reported in 20 patients, and there was a corresponding significant reduction in narcotic medication use for control of their pain. Comiter⁵⁷ also reported that interstitial cystitis patients treated with neuromodulation improved in regards to pain, with average pain scores decreasing from 5.8 to 1.6.

Although these results are encouraging, the follow-up is still relatively short. Techniques and generators with multiple electrodes derived from spinal cord stimulation using multiple quadripolar electrodes have also been used, placed via a cephalocaudal approach.⁸ Feler et al.³⁷ reported using an antegrade placement of four quadripolar electrodes with two following the course of S2 and the second medial pair overlying the S3 and S4 roots; they had treated 40 patients with interstitial cystitis and other pelvic pain and obtained an average reduction of visual analog pain scores of 55%.

Other targets for pelvic neuromodulation include posterior tibial nerve and the pudendal nerve both of which are derived from several sacral nerve roots. A theoretical advantage of stimulation of the peripheral nerves is that more segments of the sacral cord can thus be exposed to afferent stimulation. The posterior tibial nerve in current practice is stimulated by repeated sessions of temporary percutaneous needle placement just above the medial malleolus. This has been reported to improve symptoms of voiding dysfunction, as well as chronic pelvic pain.

One multicenter trial reported ~70% of patients improved, but the degree of improvement in general did not reach >50% improvement, the benchmark used in sacral nerve root studies.⁵⁸ A second multicenter trial reported an objective success rate of only 36%. Subjects with a low SF-36 baseline score on the mental component were more likely to fail.⁵⁹ A study from Spain, however, reported that 14 or 21 patients with suprapubic pain and voiding symptoms had a significant decrease of their pain with posterior tibial stimulation.⁶⁰ In general, posterior tibial nerve root stimulation has a modest efficacy, compared with transforaminal stimulation of the sacral nerve roots; the difference may be related to the intermittent rather than chronic stimulation.

More recently direct chronic stimulation of the pudendal nerve has received increasing attention. A mini-neurostimulator known as BION (Advanced Bionics, Sylmar, CA) implanted adjacent to the pudendal nerve at Alcock's canal was reported by Groen et al.⁶¹ in a small series of patients to yield significant improvement in treating patients with overactive bladder—including some in whom prior sacral nerve root modulation had failed. Spinelli and Peters and colleagues have used the tined lead used for InterStim therapy to chronically stimulate the pudendal nerve and have also reported promising results, with Peters reporting a possible superior effect of pudendal stimulation in a series of patients simultaneously implanted with both a sacral lead and pudendal leads.^{62,63} Both series were small, however, and further study is needed.

SUMMARY

Sacral nerve root neuromodulation is a relatively new but very promising method of treatment of voiding dysfunction and chronic pelvic pain previously unresponsive to traditional therapy. Improved techniques have markedly reduced the invasiveness of testing and implantation. For now, it still remains difficult to predict which patients will benefit. Staged procedures are appropriate, and chronic long-term results are still pending.

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