Neuromodulation and the Neurogenic Bladder

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Spinal cord injury (SCI) is a devastating event whose sequelae of paralysis, paresthesia, and bowel and bladder dysfunction have significant lifelong consequences. There are an estimated 12,000 new cases of SCI annually in the United States alone.¹ Neurogenic voiding dysfunction is a major contributor to the morbidity and mortality of SCI. Spina bifida and myelomeningocele are equally debilitating conditions that have a similar spectrum of symptoms including voiding dysfunction. Historically, renal disease has been the major cause of death in the paraplegic due to poor bladder management.² More recently, as a better understanding of low-pressure storage and efficient emptying has been gained, paraplegics in developed countries now die from pneumonia, septicemia, heart disease, accidents, and suicide.³ Normal lower urinary tract function consists of low-pressure storage and voluntary, coordinated expulsion of urine. Neurogenic voiding patterns range from bladder atony to hyper-reflexia with detrusor external sphincter dyssynergia (DESD) or synergia. Uncoordinated voiding or high storage pressures can cause upper tract deterioration, while high residual urine volumes can lead to recurrent urinary infections. The use of anticholinergics and clean intermittent catheterization (CIC) has led to significant improvements in the urologic health of these patients with proven efficacy and low complication rates.⁴,⁵ Despite these gains, persistent issues with regards to urinary tract infections, urethral strictures, upper tract deterioration, cost, and compliance continue to plague this patient population.

Neuromodulation is the electrical or physical modulation of a nerve to influence the physiologic behavior of an organ. In 1989, Tanagho and colleagues⁶ pioneered the initial investigations into electrical stimulation for neuromodulation. Since this early work, neuromodulation has become an important tool in the treatment of bladder dysfunction. This article reviews the application of various electrical neuromodulation techniques to treat neurogenic bladder as well as the recent literature on surgical interventions to alleviate the symptoms of neurogenic bladder and restore normal voiding.

**THE PHYSIOLOGY OF NEUROMODULATION**

The exact neural mechanisms responsible for the effects of electrical neuromodulation on the lower urinary tract are unknown. A significant amount of research has focused on the effect of sacral neuromodulation (SNM) on afferent sensory nerve fibers, with the dominant theory being that electrical stimulation of these somatic afferent fibers modulates voiding and continence reflex pathways in the central nervous system (CNS).⁷ The control of sensory input to the CNS is thought to work through a gate—control mechanism.⁸ The gate—control theory states that noxious stimuli perception does not entirely depend on the A-delta and C-fiber sensory nerves transmitting information to the...
neuromodulation, but on the pattern of peripheral nerve activity.5 A-delta bladder afferent nerve fibers project to the pontine nuclei to provide inhibitory and excitatory input to reflexes controlling bladder and sphincter function. Afferent C-fibers within the bladder are normally thought to be mechanoinsensitive and unresponsive and thus referred to as silent C-fibers. These normally inactive C-fibers may be sensitized by inflammation or infection, thus causing activation of involuntary micturition reflexes and detrusor overactivity.10 Sensory input from large myelinated pudendal nerve fibers may modulate erroneous bladder input conveyed by A-delta or C-fiber afferents at the gate—control level of the spinal cord. Detrusor hyper-reflexia then may be attributed to a deficiency of the inhibitory control systems involving pudendal afferent nerves. The success of electrical neuromodulation for detrusor hyper-reflexia may result from the restoration of the balance between bladder inhibitory and excitatory control systems.11 The stimulation of urethral afferents to facilitate the micturition reflex and stimulation of the dorsal nerve of the clitoris to inhibit bladder activity have been demonstrated in animal models for SNM.12

Another theory behind the effectiveness for SNM for hyper-reflexia is that electrical neuromodulation may alter cortical sensory areas of the brain. Blok and colleagues13 used positron emission tomography (PET) to evaluate regional cerebral blood flow in patients with chronic SNM and those patients with recently activated SNM. Their findings demonstrated activation of different areas of the cerebral cortex among patients with chronic and acute SNM. This finding also implies that the brain undergoes neuroplasticity during periods of long-term SNM in the areas of detrusor hyperactivity, awareness of bladder filling, the urge to void, and the timing of micturition. Other studies have used changes in somatosensory-evoked potentials before and after SNM to illustrate the cortical effects of SNM.14

Neuromodulation also has been used effectively for the treatment of nonobstructive urinary retention, and while the mechanism of action is not entirely clear, experimental data shed some light in this area. One such study by Schultz-Lampel and colleagues15 investigated the effects of direct sacral nerve stimulation on detrusor contractility in cats. Their data suggested that sacral nerve stimulation at low frequencies resulted in detrusor contractions. An associated rebound effect was noted with increasing amplitude of detrusor contractions with cessation of the sacral stimulus. The authors suggest that this rebound effect may be attributed to the sacral stimulus, enabling previously inhibited bladder efferent activity and thus allowing a bladder contraction. Neuromodulation also may remedy sphincter dyssynergia and the inability to void by the alteration of afferent signals delivered to the spinal cord that affect activity and basal tone of the pelvic floor.16

**SACRAL NERVE STIMULATION**

Sacral nerve stimulation long has been a reliable form of neuromodulation for various types of lower urinary tract dysfunction including overactive bladder and nonobstructive urinary retention. These two therapeutic indications make it an attractive option for treating patients with neurogenic bladder. Lombardi and colleagues17 described their experience with SNM in patients with an incomplete SCI suffering from neurogenic lower urinary tract symptoms with a mean follow-up of 61 months. They divided their study population into two groups, with one group consisting of patients with urinary retention (n = 13) and the other group consisting of patients with overactive bladder symptoms (n = 11). In the urinary retention group 9 of 13 (69%) patients reported a 50% improvement in baseline voiding parameters, with a significant decrease in the number of catheterizations and a significant increase in the frequency of void and voided volume. At the conclusion of the study, 38% of patients no longer required catheterization for bladder emptying. Among the patients with overactive bladder symptoms, an 80% reduction in daytime frequency was observed, with 3 out of 7 subjects with previous urge incontinence remaining completely dry during the study period. This study illustrates the dual efficacy of SNM for the spectrum of voiding dysfunction found in SCI patients. Other trials of SNM for neurogenic bladder have been less promising. Hohenfellner and colleagues18 described their experience with SNM among patients with neurogenic bladder dysfunction. Their patient population consisted of patients with bladder storage failure due to detrusor hyper-reflexia (n = 15), failure to empty due to detrusor areflexia (n = 11), and combined bladder hypersensitivity and detrusor areflexia (n = 1), with a mean follow-up of 89 months. In eight patients (50%), symptoms of lower urinary tract dysfunction were attenuated by 50% for 54 months (range 11–96 months). After this time period, all implants became ineffective, except in one patient. This study illustrates that while SNM may be effective for neurogenic bladder dysfunction, the results may be temporary.

**RISK WITH MAGNETIC RESONANCE IMAGING AFTER IMPLANT—WHEN IS IT SAFE?**

As the use of sacral nerve stimulators becomes more popular worldwide, there are important safety
considerations, especially with regards to magnetic resonance imaging (MRI). MRI is an important diagnostic tool for multiple medical and neurologic disorders. MRI is currently contraindicated in patients with implantable devices.19 The possible hazards of performing MRI with an implantable device such as a sacral neuromodulator include device movement, dislocation of the neurostimulator, excessive heat to the nerve, changes in programming, and damage to the neurostimulator components. Elkelini and Hassouna20 retrospectively reviewed histories of six patients who underwent a total of eight MRI examinations with sacral neuromodulation. Five examinations were of the brain, while three other examinations were of the cervical and thoracic vertebrae using a magnetic resonance system operating at a static magnetic field strength of 1.5 T. No patients reported any unusual symptoms during the examination, and imaging was not affected by the pulse generator located away from the imaged anatomic area. The pulse generators were turned off before MRI examination and when interrogated after the examination, no malfunctions were found. There was no change in the perception of stimulus once the pulse generator was reactivated, and follow-up voiding diaries revealed no changes in voiding parameters. Although the author’s findings are encouraging, the routine use of MRI with an implanted device such as Interstim (Medtronic, Minneapolis, Minnesota) still should be used with caution.

COMPLICATIONS OF SACRAL NEUROMODULATION

Complications from SNM have been well described and are usually minor adverse events. The rate of complication ranges from 12%21 to 53%22 depending on the examined series. A recent article by White and colleagues23 followed patients receiving SNM for urinary urge/frequency, urge incontinence, and urinary retention to record the incidence of adverse events and determine if there are predictive factors predisposing patients to adverse events. At a mean follow-up of 37 months, 30% of patients had experienced adverse events. Lead migration, lack of efficacy, and trauma were the most common adverse events. Significant predictors of adverse events included a history of trauma, a change in body mass index class, enrollment in a pain clinic, the duration of follow-up, and a history of adverse events.

PUDENAL NEUROMODULATION FOR NEUROGENIC BLADDER

The pudendal nerve is a peripheral nerve that is composed mainly of afferent sensory fibers from sacral nerve roots S1, S2, and S3. Most afferent sensory fibers are contributed by S2 (60%) and S3 (35%) according to afferent activity mapping procedures.24 Consequently, the pudendal nerve is a major contributor to bladder afferent regulation and bladder function. Pudendal nerve entrapment often leads to significant voiding dysfunction, including urinary incontinence and detrusor hyperreflexia.25 Because the pudendal nerve carries such a large percentage of afferent fibers, neuromodulation of the pudendal nerve is an attractive option for refractory detrusor hyperreflexia. Opisso and colleagues26 compared patient-controlled pudendal nerve stimulation with automatic stimulation to treat neurogenic detrusor overactivity. A total of 17 patients with neurogenic detrusor overactivity underwent three cystometric filling trials. The first cystometry was used to determine bladder capacity. The second cystometry was done with automatic electrical stimulation of the pudendal nerve when the bladder reached a threshold pressure of 10 cm H2O above the mean detrusor pressure. The third filling cystometry was done with patients controlling the pudendal stimulation and asked to begin stimulation when they could sense the onset of an uninhibited bladder contraction. Automatic and patient-controlled pudendal nerve stimulation resulted in greater bladder capacity in all subjects and inhibited more than an average of 2 detrusor contractions per filling. The authors suggest that based on their findings patients with neurogenic detrusor overactivity may be able to use patient-controlled stimulation of the pudendal nerve to increase bladder capacity and prevent uninhibited detrusor contractions. Spinelli and colleagues27 described their experience with pudendal nerve stimulation using a device with a quadrupolar tined lead placed at Alcock canal in 15 patients with neurogenic bladder. In this study, the average number of incontinent episodes among this group of patients decreased from seven to three episodes per day. Eight patients became continent during the screening phase of the study, and four patients had a greater than 50% improvement in the number of incontinent episodes experienced per day. Urodynamic evaluation in seven patients revealed a significant increase in detrusor capacity and a decrease in maximum detrusor pressure. The authors suggest that based on these preliminary data, pudendal nerve stimulation is an effective therapeutic alternative for neurogenic overactive bladder patients who are nonresponders to antimuscarinic drugs and in whom traditional sacral neuromodulation has had poor results. The authors also point out that the minimally invasive nature of pudendal nerve
stimulation using the quadrupolar tined lead is an attractive alternative to more invasive procedures such as bladder augmentation. Currently at the authors’ institution, the most common indication for pudendal neuromodulation is for patients who have had failure of sacral neuromodulation. The placement of the lead is done via a posterior approach and requires electrophysiologic monitoring of the pudendal nerve action potentials intraoperatively to confirm pudendal stimulation.

NEUROMODULATION OF THE POSTERIOR TIBIAL NERVE FOR NEUROGENIC BLADDER

The posterior tibial nerve is a peripheral mixed sensory—motor nerve that originates from spinal roots L4 through S3, which also contribute directly to sensory and motor control of the urinary bladder and pelvic floor. Stimulation of the posterior tibial nerve was pioneered by Stoller and colleagues with the introduction of a nerve stimulator, which delivers electrical stimulation to the posterior tibial nerve via a 34-gauge needle just cephalad to the medial malleolus. Multiple studies have demonstrated that posterior tibial nerve stimulation (PTNS) shows some efficacy in treating symptoms of detrusor hyperactivity and altering urodynamics in patients with overactive bladder. A recent article prospectively examined the use of PTNS among children with voiding dysfunction with 2 years of follow-up. Of the 43 patients in the trial, 12 had neurogenic bladder due to spinal dysraphism at the sacral level. Patients were evaluated before and after PTNS with a voiding diary and noninvasive voiding measurements. Relief of lower urinary tract symptoms was significantly greater in patients with non-neurogenic bladder than those with neurogenic bladder (78% vs 14%). The authors suggest that the variable results among patients with neurogenic bladder resulting from spinal dysraphism may be due to the variable neural lesions found among these patients and that improved patient selection might lead to more impressive results.

FINETECH-BRINDLEY POSTERIOR/ANTERIOR STIMULATOR

Research regarding electrical stimulation to improve micturition in SCI patients has been ongoing for the last 50 years. In 1969, Brindley developed a device to stimulate sacral roots at the level of the cauda equina. The first Brindley stimulator was implanted in a patient in 1978. Although the first implants did not involve posterior sacral rhizotomy, lesions to these nerves during surgery led to the advantage of leaving the patient’s bladder completely areflexic and restoring normal bladder compliance and curing reflex incontinence. Subsequently, placement of the Brindley stimulator was combined with sacral posterior rhizotomy. The deinnervation step is skipped in cases of genital sensation and reflex erections. Over a retrospective review of 500 patients with a Brindley stimulator, 411 were still in use with the patients pleased. Ergon and colleagues reviewed their experience with 93 SCI patients with sacral anterior root stimulators combined with posterior sacral rhizotomy. They reported that 83 patients used their stimulators for micturition, and 82 were fully continent. The major limitation to this form of neuromodulation is that it requires an intact neural pathway between the sacral cord nuclei of the pelvic nerve and the bladder. This is not always the case, especially in children with lap belt injuries that result in lower motor neuron lesions.

HEMILAMINECTOMY AND VENTRAL ROOT MICROANASTOMOSIS, THE XIAO PROCEDURE

Kilvington first described the idea of bladder reinnervation in 1907, but he failed to demonstrate any response after lumbar-to-sacral reinnervation in a canine model. Subsequently, Xiao’s landmark study with rats confirmed the assumption that the efferent root of a somatic reflex arc could regenerate into the autonomic efferent root that controls the bladder. A total of 24 rats underwent a lateral hemilaminectomy. After transaction of L4 and L6 ventral roots, the proximal end of the L4 ventral root was attached to the L6 ventral root. After allowing 3 months for axonal regrowth, 15 rats underwent neurophysiological experiments, and 6 rats had horseradish peroxidase (HRP) neural tracing studies. The final three rats were saved for a year for long-term observation. Of the 15 rats, 12 were viable for study, and in all of them, a bladder detrusor contraction was elicited by L4 electrical stimulation. This contraction generated an average of 38 plus or minus 7 cm H2O of intravesical pressure. The HRP tracings demonstrate histologically the successful regeneration of somatic motor axons into an autonomic efferent root. In four rats, somatic motor neurons in the L4 ventral horn were positively labeled with the HRP, while the remaining two had traces in left pelvic ganglia neuron axons. The long-term specimens proved the functionality of the reflex arc. Electrical stimulation of the distal sciatic nerve caused a bladder contraction, as did scratching of the L4 dermatome. This then was tested on six cats by intradural microanastomosis of the left L7 ventral root (VR) to the S1 VR. This created a skin-CNS-bladder...
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reflex that uses the cutaneous afferent signal to trigger the micturition reflex arc. After 7 months of recovery, cutaneous stimulation of the L7 dermatome created a strong detrusor contraction that resulted in an elevation of bladder pressure (45 ± 8 cm H2O). Of note, the four long-term subjects exhibited no consequential motor deficits.

The success in animal models encouraged human trials. Xiao described how he created a somatic-CNS-autonomic pathway in 15 patients with hyper-reflexic neurogenic bladders and DESD secondary to complete suprasacral SCI. A microanastomosis was made between the L5 ventral root and the S2/3 ventral root to allow the motor axons to reinnervate the autonomic preganglionic nerves. These patients were followed with postoperative urodynamic evaluations for an average of 3 years postoperatively. In 10 of the 15 patients, bladder function, including storage and emptying, was recovered. Similar to the animal models, cutaneous stimulation of the appropriate dermatome instigated the skin-CNS-bladder reflex, causing voiding. Interestingly, 4 of these 10 patients had resolution of their hyper-reflexia with DESD to normal voiding with low postvoid residuals. The remaining six had no change in their DESD, but they were able to use the new reflex to successfully void with low residuals. The Xiao procedure then was performed on 20 children with spina bifida. Preoperatively, 14 had an areflexic detrusor with small bladder capacity, open urethral outlet and incontinence. The remaining six suffered from hyper-reflexic bladder with DESD, similar to the suprasacral SCI patients. Seventeen of the 20 patients (85%) recovered acceptable bladder storage and function. Those with atonic bladders had an average increase of bladder capacity of 94 mL to 177 mL and a decrease in postvoid residuals (70 mL–24 mL), with only two patients failing to see any improvement. Of those with DESD, five were able to void spontaneously with a significant decrease in mean detrusor pressure. Five of the 20 patients developed a motor deficit in L4 or L5, ranging from slight muscle weakness to visible foot drop. No other complications were reported. It was noted that from a technical perspective, the spina bifida cases were more challenging than SCI secondary to the abnormal neuroanatomy.

NORTH AMERICAN EXPERIENCE WITH THE XIAO PROCEDURE

There have been attempts to replicate the Xiao procedure in the United States. The first trial involved two traumatic SCI patients, a complete T6 and T11, respectively, causing neurogenic detrusor overactivity with DESD. Prior to the nerve rerouting surgery, the patients were being managed by CIC and anticholinergics. An intradural anastomosis was unilaterally made between the ventral root of L5 to S3. At 6 months after operating, detrusor contractions were elicited via cutaneous L5 stimulation in both patients as well as a significant decrease in detrusor overactivity. By the 15-month follow-up, both patients were completely off anticholinergics and CIC. Cystometrygram studies show that L5 stimulation generates a detrusor contraction of 59 cm H2O, a Qmax of 8 cc/s with no DESD. Voided volume was 150 cc, and postvoid residual was 200 cc/s. There were no significant complications in this small cohort.

A larger study was performed in a group of nine spina bifida patients, mean age 8 years (range 6–37 years). All patients were on a CIC regimen preoperatively and underwent a rigorous neurologic, urologic, urodynamic, and lumbar–sacral examination before surgery. The Xiao anastomosis was made between the unilateral ventral lumbar root and S3. There were no surgical complications. At 1 year after operating, seven out of nine patients were able to generate at least a 10 cm H2O rise in detrusor pressure with cutaneous stimulation of the dermatome. Mean PVR was 119 cc (range 10–380 cc), Qmax of 10 cc/s (range 4–25 cc/s). No patient achieved complete urinary continence, and only two were able to completely stop CIC. Two unintended benefits were noted. First, the bowel function of the patients improved significantly. The procedure has changed their quality of life enough to the point where seven out of nine would undergo it again. The other peculiar anecdote is a return of bladder sensation. Many subjects reported the return of early filling sensation of both the bowel and bladder. Unfortunately, one patient did suffer from foot drop that significantly worsened her gait. There were no other significant neurologic complications at 1-year follow-up, and changes in bowel and bladder function continue to improve with longer follow-up.

SUMMARY

Neuromodulation is changing the management of voiding dysfunction. Techniques using both electrical and mechanical stimulation are being researched to help correct the underlying bladder and bowel dysfunction. Advances in neuromodulation techniques may allow the clinician to abandon irreversible destructive/reconstructive procedures such as bladder augmentation and urinary diversion. Further research into this field...
is needed to expand understanding of urology and improve the treatment of patients.

REFERENCES