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Expanding Indications for Neuromodulation

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Neuromodulation to treat voiding dysfunction has been studied for decades. In 1997, sacral nerve modulation (InterStim, Medtronic, Minneapolis, MN) was approved by the Food and Drug Administration for urinary urge incontinence, urinary urgency-frequency, and nonobstructive urinary retention. The mechanism of action remains unknown, yet neuromodulation has been effective in treating patients who were otherwise considered candidates for radical surgery or deemed simply incurable. Since its inception, widespread use for approved conditions has led to incidental improvements in other areas. Research is ongoing to channel the potential of neuromodulation into other applications.

The major frontiers for sacral neuromodulation in adults are interstitial cystitis and chronic pain syndromes (ie, pelvic pain, prostadynia, epididymo-orchalgia, and vulvodynia); neurogenic bladder from spinal cord injury; fecal incontinence and constipation; and erectile dysfunction. Projects are ongoing to evaluate the efficacy of neuromodulation in children with voiding dysfunction. Other areas that have shown promise, albeit outside the realm of urologic practice, are migraine headaches and chronic angina pectoris.

Interstitial cystitis

Interstitial cystitis is a painful and frequently debilitating condition of the urinary bladder. There are an estimated 700,000 cases of interstitial cystitis in the United States. Its symptoms include pelvic pain, dyspareunia, urinary urgency and frequency, nocturia, and small voided volumes with small bladder capacity. Although some of these characteristics individually are indications for neuromodulation, currently neuromodulation is not approved for the pain component of interstitial cystitis. Pharmacologic therapy for interstitial cystitis includes pentosan polysulfate, antihistamines, antidepressants, intravesical instillations, and narcotic pain medications. Cystoscopy with bladder hydrodistention can provide temporary treatment in a subset of patients. Radical surgery (cystectomy, augmentation cystoplasty) is rarely indicated and may not provide symptomatic relief because of centralization of pain [1].

In 2003, Comiter [2] performed a prospective study that evaluated sacral neuromodulation for the treatment of refractory interstitial cystitis. At a mean of 14 months follow-up, urinary frequency decreased from 17.1 to 8.7 voids per day, mean voided volume increased from 111 to 264 mL, and pain decreased from 5.8 out of 10 to 1.6 out of 10. Ninety-four percent of subjects implanted demonstrated a sustained improvement in symptoms.

Peters and Konstandt [3] have shown that sacral neuromodulation decreases narcotic requirements in refractory interstitial cystitis. Twenty-one subjects with the symptom complex of urinary urgency, frequency, and pelvic pain had cystoscopically confirmed interstitial cystitis. The mean age was 45.5 years and the subjects had failed on average six previous IC therapies. Eighteen subjects were on chronic narcotics before implantation with InterStim and three were on nonnarcotic analgesics. Narcotic requirements before and after the implantation were standardized to intramuscular morphine dose equivalents. Subjects were asked to rate their pelvic pain after implantation on a seven-point scale ranging from "markedly

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worse" to "markedly improved" with "no change" centered on the scale. With a mean follow-up of 15.4 months from implantation of the permanent generator, 20 (95%) of 21 patients reported moderate or marked improvement in pain after InterStim; the remaining subject reported no change in her pelvic pain. Mean narcotic use decreased from 81.6 to 52 mg/d (35%; $P = .015$). Four of 18 subjects stopped narcotics altogether. Patients were overwhelmingly satisfied with the results of their trial of neuromodulation compared with their prior therapies.

In addition to the clinical evidence supporting the use of sacral neuromodulation for the treatment of interstitial cystitis, Chai et al [4] reported that urinary levels of antiproliferative factor and epidermal growth factors that have been shown to be elevated in interstitial cystitis normalized in subjects with interstitial cystitis after a trial of sacral neuromodulation.

Chronic genitourinary pain

Chronic pain conditions pose a very difficult clinical challenge. Multidisciplinary approaches are often used with highly variable results. Chronic pain leads to psychologic disturbances and ultimately to a pain cycle, which becomes nearly impossible to break. Sacral neuromodulation has been used to control a variety of forms of genitourinary pain.

Siegel et al [5] performed a feasibility study in patients with intractable pelvic or genitourinary pain. Patients were excluded if they had definable neurologic or pelvic pathology. Neuromodulation decreased the severity and duration of the pain with improvement in quality of life. Similarly, Everaert et al [6] treated patients with refractory pelvic pain with sacral neuromodulation. They found that 60% of those tested were candidates for a permanent implant and with a mean of 36-month follow-up, all patients maintained a greater than 50% improvement in their pain levels.

Chronic, nonbacterial prostatitis is the most common urologic diagnosis in men less than 40 years old. Typical symptoms include persistent urinary urgency, frequency, dysuria, poor urinary flow, and perineal pain in the face of negative bacterial cultures from the urine or expressed prostatic secretions. Treatment of this condition is often refractory to multimodal therapy. In addition, epididymo-orchalgia is a similar condition where pain in the testicle is prominent without positive findings on physical examination, urinalysis, or scrotal imaging. Feler et al [7] reported a 44-year-old man with a 6-year history of chronic epididymitis and prostatitis. Pain medications, antibiotics, and antidepressants were unsuccessful in improving his condition. Sacral nerve stimulation provided a 75% improvement in his painful condition.

Vulvodynia consists of chronic vulvar discomfort, including burning, itching, and dyspareunia. Physical examination and vulvar biopsies fail to explain the clinical scenario. Again, Feler et al [7] reported a 71-year-old woman with a 9-year history of vulvodynia, unimproved by medications, biofeedback, and laparoscopic interventions. Sacral root stimulation provided excellent pain relief.

Sacral neuromodulation has been used in each of these chronic pain conditions. Early case reports and small series have shown dramatic reduction in visual analog pain scores and a significant reduction in narcotic use.

Neurogenic bladder caused by spinal cord injury

Spinal cord injury is a leading cause of neurogenic voiding dysfunction. Symptoms are variable, but commonly seen are urinary tract infections, urolithiasis, reflux, obstruction, and incontinence. The goals of management for neurogenic bladder are to increase bladder capacity, control the bladder storage pressure, protect the upper urinary tract, and prevent incontinence. After spinal shock resolves, detrusor hyperreflexia generally develops.

Andrews and Reynard [8] reported a case of a 64-year-old man with T8 paraplegia from spinal artery thrombosis. His motor and sensory dysfunction ultimately resolved, but he was left with urinary urgency and urge incontinence. Self-catheterization and anticholinergic therapy were unsuccessful in improving the symptoms. Urodynamics revealed detrusor hyperreflexia. Percutaneous tibial nerve stimulation, a minimally invasive form of neuromodulation, was performed after baseline bladder capacity was measured at 165 mL. Cystometric capacity after stimulation increased to 310 mL. Serial measurements were performed 3 weeks later and cystometric capacity had returned to baseline. Stimulation was again performed and cystometric capacity quickly increased to 300 mL.

Vastenholt et al [9] reported a series of 37 patients (average age: 43) with spinal cord injury who underwent implantation of sacral anterior

root stimulators. At 7 years follow-up, 87% of the study group continued to use their stimulator for control of micturition and 60% used the stimulator for its benefits with respect to defecation. Of the 32 male patients, 65% were incidentally able to achieve a stimulator-induced erection. Overall improvement in incontinence was 73%. Urinary tract infections decreased by 87% after implantation. Forty-one percent never developed an infection after their stimulator was implanted.

Fecal incontinence and constipation

Bowel function is another area of research in the field of neuromodulation. Both fecal incontinence and chronic constipation are difficult clinical entities. Fecal incontinence disables a patient's personal and professional life and can lead to severe psychologic disorders. It is reported to affect 1% to 7% of the general population greater than 65 years of age. Current therapy consists of pharmacologic modalities, biofeedback, and surgery.

Ripetti et al [10] treated patients with sacral neuromodulation from 1998 to 2000. Presuming an anatomically intact anal sphincter, neuromodulation has been shown to improve incontinence and obstructive defecation symptoms. Ganio et al [11] showed sacral neuromodulation to decrease the number of unsuccessful defecation attempts and a reduction in the difficulty of defecation. Further studies have shown that an increase in resting rectal pressure, voluntary contraction pressure, and maximum squeeze pressure can be obtained with neuromodulation. Also demonstrated was a reduction in pressure needed for rectal sensation, first pressure of urge to defecate, and a lowered rectal volume of urgency. Shafik et al [12] reported 78% improvement in fecal incontinence as measured by questionnaire and physiologic-rectometric analyses.

In addition, Chang et al [13] treated a 25-year-old female patient who complained of intractable constipation for 10 years. Colon transit time study and defecography showed nonspecific findings. Anorectal manometric findings revealed impaired rectal sensation. Rectal sensory threshold volumes for desire and urge to defecate and maximal tolerated volume were greatly increased. She was treated by electric stimulation therapy for the purpose of improving impaired rectal sensory function. After 14 sessions of electric stimulation therapy, her constipation symptoms improved dramatically. Furthermore, the desire and urge threshold volumes were remarkably decreased.

Erectile dysfunction

Electrical stimulation of the cavernous nerve results in increased arterial flow, relaxation of cavernous muscles, and venous outflow restriction, producing erection. Cavernous nerve stimulation has been demonstrated to produce penile erection in monkeys [14], dogs [15], and rats [16].

In 16 men undergoing retropubic radical prostatectomy, Lue et al [17] applied electrical stimulation to the prostatic apex bilaterally, producing visible erection in the retropubic radical prostatectomy population. The authors concluded that it is indeed feasible to produce penile erection through intraoperative electrical stimulation of the cavernous nerves.

Shafik [18] implanted a cavernous nerve stimulation device in a series of 15 men for the treatment of erectile dysfunction. Cavernous nerve stimulation at a frequency of 10 Hz led to penile tumescence and an increase in intracavernous pressure but poor rigidity. When the stimulation frequency was increased to 60 Hz, penile tumescence and rigidity and intracavernous pressure increased, and full erection was achieved. Additionally, Shafik's study demonstrates that unilateral cavernous nerve stimulation is sufficient to induce erection.

Children

Similar to adults, children are faced with various degrees of lower urinary tract dysfunction. Incontinence, overactive bladder, and urinary retention are the most common conditions. Nonneurogenic, neurogenic bladder (Hinman syndrome) causes severe voiding dysfunction and often upper-tract deterioration. The underlying cause is unknown. Children often require management with intermittent catheterization and anticholinergics. Unfortunately, this treatment modality is not uniformly successful and major reconstructive surgeries can be required to manage symptoms. It makes sense to consider neuromodulation before any irreversible reconstruction is considered.

Hoebeke et al [19] reported their early experience with transcutaneous neuromodulation in children with refractory detrusor hyperactivity. Forty-one children, with an average age of 10, had

urodynamically proved detrusor hyperactivity and failed anticholinergics. Surface electrodes were placed at the S3 foramen and daily 2-hour stimulation at 2 Hz was applied. After 1-month of trial stimulation, those responding to therapy continued for a total of 6 months. A positive response was seen in 28 of 41 children. After 6 months of therapy a significant increase in bladder capacity, decrease in voiding frequency, and decrease in incontinence episodes were noted.

De Gennaro et al [20] used percutaneous tibial nerve stimulation as a method of treating lower urinary tract symptoms in children 4 to 17 years old. Thirty-four–gauge needles are inserted two fingerbreadths cephalad to the medial malleolus. Plantar flexion or fanning of the toes confirmed proper needle placement. Twelve sessions were performed. They reported 80% improvement in the pediatric population with overactive bladder, 50% improvement in incontinence symptoms, 62% improvement in cystometric bladder capacity, and 71% improvement in children with urinary retention. No adverse events were noted and fear of needle insertion was tolerable and improved considerably over time.

Humphreys et al [21] recently reported their experience of implantation of a sacral nerve stimulator in 16 children with refractory voiding dysfunction. Children with a mean age of 11 years (range: 6–15) with dysfunctional voiding, nocturnal enuresis, wetting, urinary tract infections, bladder pain, urinary retention, dysuria, urgency, frequency, constipation, or fecal incontinence underwent urodynamics. Patients underwent testing with sacral nerve stimulation in a staged fashion and were implanted with a permanent generator. The subjects were followed for a mean of 13 months. Urinary incontinence resolved or improved in 75% (9 of 12); nocturnal enuresis improved in 83% (10 of 12); urinary retention improved in 73% (8 of 11); bladder pain improved in 56% (5 of 9); and constipation improved in 78% (7 of 9). The number of daily medications decreased by 2.8 medications per patient. The overall patient satisfaction was 64% and parent satisfaction was 66%. Two devices were explanted.

Nonurologic frontiers

Angina pectoris

Studies are underway and small series are published lauding the potential use of neuromodulation in the treatment of chronic, refractory angina pectoris. Cardiac syndrome X is defined as typical anginal chest pain with normal coronary anatomy. In a study by Jessurun et al [22] transcutaneous electrical nerve stimulation was performed on eight patients with heterogeneous myocardial perfusion and no esophageal abnormalities. Myocardial perfusion and anginal symptoms were evaluated. Following neuromodulation therapy, there was a significant reduction in episodes of angina and nitroglycerin intake. Perfusion was increased and coronary vascular resistance was decreased.

Chronic migraine

Matharu et al [23] has performed implantation of suboccipital neurostimulators in patients with the diagnosis of chronic migraine headaches. The electrodes were placed superficial to the cervical muscular fascia at the level of the first cervical spine. Neurostimulators were implanted in eight patients with intractable headache pain. Four patients reported complete headache suppression, with rare breakthroughs. Two patients reported very good results, with continued occasional breakthrough headaches. Two final patients reported 50% to 75% reduction in severity, although the frequency of headaches continued. All patients reported a significant reduction in the need for headache medications. Follow-up has been from 7 months to 3 years, and the results have been maintained.

Summary

Neuromodulation in one form or another has been studied for decades for various disease states. Although its mechanism of action remains unexplained, numerous clinical success stories suggest it is a therapy with efficacy and durability. Controlled studies have led to the approval of sacral neuromodulation for urinary urgency and frequency, urinary retention, and urinary urge incontinence. The future holds hopeful possibilities for the application of neuromodulation, namely in the areas of interstitial cystitis, intractable pain syndromes, fecal incontinence and constipation, spinal cord injury, and erectile dysfunction. Neuromodulators have also been used in nonurologic conditions, including chronic headaches and intractable chest pain. In adults and children, in the neurologically intact and neurologically impaired, neuromodulation has

been shown to improve the quality of life of those suffering chronic disease states.

Neuromodulation is changing the future of urology. Treatment of voiding dysfunction and likely other disorders, such as pelvic pain, sexual dysfunction, and bowel disorders, will no longer rely only on medications that are "OK" or destructive-reconstructive procedures that suffer from significant complications. Rather, by modulating the nerves, the urologists will treat these disorders in a minimally invasive fashion and neuromodulation will become the first-line therapy before any major surgery is undertaken.

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