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Neuromodulation for Neurogenic Bladder

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Abstract

Although neuromodulation is well established for the treatment of non-neurogenic lower urinary tract symptoms, recent literature supports its use in the patient having LUTS associated with a neurologic condition. Sacral neuromodulation, in particular, may see new use as a modality to facilitate neurologic remodeling in spinal cord injured patients as well as children. As a therapeutic option, sacral neuromodulation and dorsal genital nerve stimulation may one day become more effective and more efficient utilizing the concept of closed-loop feedback, where electro-neurogram and bladder pressure data are incorporated into stimulation routines. In addition, some older therapies are reviewed that have recently demonstrated success in this patient population.

Introduction

The prevalence of lower urinary tract symptoms (LUTS) in subjects residing in the US, UK, and Sweden is surprisingly high according to data from the 2009 EPILUTS project. 72.3% of male respondents reported “at least sometimes” being bothered by one of the LUTS listed, and 76.3% of women reported being bothered. [1]. The majority of these conditions are idiopathic, but at times there is a neurogenic origin for the LUTS, and this may affect treatment.

When neuromodulation was first investigated for the treatment of LUTS it was widely thought that an intact neurologic system was necessary for such therapy to be effective. Because of this, patients having a neurologic cause for the LUTS were not included in the initial large scale studies investigating sacral nerve root stimulation [2], including the FDA approval trial, known as MDT-103 [3]. Early experience with sacral neuromodulation in patients having a neurogenic cause for LUTS was disappointing, with one early series noting a loss of benefit over a follow up of 54 months in all but 1 of 12 patients [4]. Since then, multiple authors have demonstrated that neuromodulation is effective in treating neurogenic bladders [5–8] calling into question this previously accepted dogma. Many new methods to manipulate the genitourinary (GU) nervous system have become available in the past decade, and recent basic science and animal studies suggest more innovative therapies are on the way.

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Define Neurogenic Bladder

Common causes of neurogenic voiding dysfunction include spinal cord injury, multiple sclerosis, Parkinson's disease, cerebrovascular accident, and diabetes mellitus. Certain congenital forms of neurogenic bladder, such as myelomeningocele, have recently become more relevant in the adult population as these patients are living longer, more active lives due to multiple advances in the treatment of their co-morbidities.

Basic Science – What Have We Learned In The Past Few Years About The Genitourinary Nervous System?

For years clinicians treating patients with voiding dysfunction have noted a relationship between constipation and urinary symptoms, leading to speculation that there is some pelvic nerve cross talk. Recently investigators have demonstrated the existence of pelvic organ cross talk in animal models [9–11]. In addition to describing the architecture of the pelvic nervous system, new insight illuminating the function of the GU nervous system has also appeared in the literature. Using a cat model, investigators have demonstrated sacral nerve stimulation (dorsal root) inhibits reflex bladder activity even if hypogastric or pudendal nerves are transsected, suggesting that this reflex activity occurs in the central nervous system by inhibiting the ascending or descending pathways of the spinobulbospinal micturition reflex [12]. The cat model developed by the investigators demonstrated inhibition with sacral afferent stimulation whether the sympathetic and pudendal nerves were intact or not. This gives new evidence that sacral neuromodulation may work primarily through the CNS. Three other competing hypotheses are that SNM works by direct activation of motor fibers innervating the external urethral sphincter, thereby increasing its tone, or that it increases sphincter afferent firing that then modulates bladder sensory or motor pathways in the CNS. Finally, by stimulating afferents directly, reflexes may be activated to, in turn, activate the sympathetic efferents, inhibiting bladder contractions, and simultaneously stimulating the external sphincter tone via CNS.

Remodeling of the function and structure of the brain has also been investigated. Recent studies utilizing PET scanning and regional blood flow changes in the brain have demonstrated significant differences in those who have undergone neuromodulation for a period of >6 months when compared with those whose stimulator was activated for the first time in the PET scanner [13]. This suggests an additional role for sacral neuromodulation as a moderator for brain remodeling.

Before determining that neuromodulation is appropriate for the patient suffering from neurogenic voiding dysfunction it is important to determine the nature of the voiding dysfunction. This can range from urinary urgency and frequency, as is often seen with Parkinson's disease, stroke, and multiple sclerosis, to complete urinary retention, as often seen in spinal cord injury and myelomeningocele. Urinary incontinence may or may not be a symptom of the neurogenic bladder. It is important to keep in mind that, in addition to the significant quality of life issues, there are life threatening issues that must be considered, such as urosepsis and renal failure.

TREATMENT

Options for treating patients with LUTS secondary to neurologic dysfunction include behavior modification, physical therapy, treatment of the underlying neurologic disorder in relapsing conditions such as Multiple Sclerosis (MS), and medication. When these conservative measures fail, it is reasonable to consider neuromodulation. It is important to note that regardless of the form of neuromodulation, good practice for neurogenic patients still includes regular follow up with laboratory tests and radiographic and urodynamic studies so that upper tract deterioration can be detected, if it develops [14].

SACRAL NEUROMODULATION

Over the past decade, sacral neuromodulation has become the dominant form of neuromodulation in the GU nervous system. It was once thought that sacral neuromodulation would not work properly for patients suffering from neurogenic voiding dysfunction because the neurologic pathways were not intact. This has been challenged in recent literature and sufficient evidence exists to demonstrate equivalent efficacy whether the cause of the voiding symptoms is neurogenic or not [5–7,15]. Recently, Peters and colleagues have demonstrated no difference in 340 consecutive patients, 71 of whom had a neurogenic diagnosis concomitant with the voiding dysfunction and some with non-neurologic causes. Endpoints included generator implantation rate (88% vs. 89%, respectively, p=0.82), multiple validated questionnaires, and the Global Response Assessment [8]. It is important to note this was a retrospective chart review, and the specific diagnosis was named in only 45/71 patients with a neurologic diagnosis. Reduction in incontinence episodes interestingly did not reach statistical significance in the neurologic diagnosis group (6.7 to 5.5 after24mo.) but did in the non-neurologic group (6.3 to 5.2). More of the neurologic diagnosis group reported satisfaction on the Global Response Assessment than those without a neurologic problem (81% vs 54%) [8].

Mentioned earlier in the basic science section, the concept of neurologic remodeling has added a new potential role for sacral neuromodulation. Some theorize that neuromodulation has the ability to remodel the brain and possibly achieve permanent benefit, even after stimulation has ceased. One disease state where this may be particularly beneficial is acute spinal cord injury. Sacral neuromodulation has been used in patients with neurogenic bladder after spinal cord injury early during the spinal shock period, when the bladder is atonic. This was suggested in a recent investigation by Sievert and colleagues who performed urodynamic studies on 10 patients who received early bilateral S3 leads. 6 patients were also included as control patients, but were not blinded nor randomized to that group. The controls demonstrated lower bladder capacity (294cc vs. 582cc) and more urinary tract infections (3.8 UTIs per year vs. 0.5) over 26 months of follow up [15] ●. Interestingly, erectile function and bowel function were also improved in the early neuromodulation group.

In addition to acute spinal cord injury patients, children may also exhibit neurologic remodeling. Reinberg and colleagues note this phenomenon in their experience in children with dysfunctional elimination syndrome, in which 11% (13 of 118 children) are able to be explanted with continued resolution of symptoms at an average of 40.9 months [16]. More

investigation is needed as none of these were controlled studies, but rather retrospective reviews. This type of investigation should begin with animal studies. With this in mind, pudendal neuromodulation has been noted in dogs to have a protective effect on the bladder if instituted within a month of the surgically induced spinal cord injury, but not if instituted 6 months after the injury, further supporting the beneficial effect of early neuromodulation [17] ●●.

S3 Sacral neuromodulation has been used in children with good results, some with neurogenic voiding dysfunction. Salvage pudendal neuromodulation was able to successfully treat 7 patients who were refractory to S3 neuromodulation. Investigators noted good short-term results (78% full or partial response) and satisfactory long-term results (73% response). Some of these children had myelomeningocele, but the majority were not neurogenic in etiology. The authors suggest that pudendal nerve stimulation is a feasible salvage solution even for children, and can be useful in cases when S3 implantation is impossible or unsuccessful. [18].

Improvements To Sacral Neuromodulation

The cardiac pacemaker was the first electrical stimulator to enjoy widespread implantation in the human body. Significant improvements were achieved in cardiac pacing when devices became responsive to real-time feedback from the heart, making therapies such as implantable cardiac defibrillation possible [19]. This feedback, known as closed loop feedback, does not currently exist for the bladder. Some investigators have demonstrated that it is possible to distinguish between 3 levels of bladder fullness in rats by attaching cuff electrodes to nerve roots carrying primary afferent neural activity from bladder mechanoreceptors. [20] ●●. Others have developed implantable pressure sensors that may one day be used to provide feedback to stimulation devices [21,22]. Closed loop feedback has been tested in humans with spinal cord injury, demonstrating some improvements in bladder capacity and compliance when compared with continuous (conventional) stimulation (173mL increase in capacity vs. 230mL) [23]. Recently this concept has also been demonstrated in dogs with similar efficacy, including an increase in bladder warning time from 10 seconds to 360 seconds. Bladder capacity improved from 70mL in the dogs receiving continuous afferent stimulation to 98mL in the dogs receiving functional electrical stimulation. The capacity went up even further to 103mL in those receiving both continuous afferent stimulation and functional electrical stimulation together [24] ●.

Work has been done with conditional neuromodulation in human subjects having complete and incomplete spinal cord injuries. The dorsal genital nerve was stimulated when filling pressures or detrusor contractions were sensed that exceeded 8–12 cm H_2O above baseline. This lead to an increase in maximum cystometric capacity and less energy used for stimulation in the conditional group, which may have implications for battery life in implanted devices. Continuous and conditional stimulation increased bladder capacity by 63 mL (36%) and 74 mL (51%), respectively ($P < 0.05$), compared to no stimulation.[25]

Pudendal Neuromodulation

Pudendal neuromodulation is typically used as second line therapy in the treatment of non-neurogenic voiding dysfunction, but has been used with promising results recently for patients having a variety of diagnoses. One of the early reports of pudendal neuromodulation involved 15 patients having urge incontinence secondary to neurogenic bladder. The authors noted an improvement from 7 incontinence episodes daily to 2.6 [7]. Peters and colleagues compared pudendal neuromodulation with sacral neuromodulation in a randomized blinded cohort of 22 interstitial cystitis patients, with 77% of the pudendal stage 1 leads having a more effective trial than the sacral leads, suggesting pudendal neuromodulation may be more effective in this patient population [26]. Recent animal investigations failed to demonstrate that bilateral pudendal neuromodulation was significantly better than unilateral pudendal neuromodulation following surgically induced spinal cord injury in rats with urinary retention [27]. Pudendal neuromodulation has been reported to be effective for neurogenic urinary retention secondary to cerebral palsy as well [5].

IntraVesical Electrical Stimulation (IVES)

Intravesical electrical stimulation (IVES) is among the more mature neuromodulation techniques described to stimulate the bladder via catheter based electrode which has recently shown modest promise in patients suffering incomplete spinal cord injury and non-obstructive neurogenic urinary retention. The technique as described by Lombardi and colleagues includes at least 28 days consecutive stimulation sessions for subjects having incomplete spinal cord injury. The authors report a success rate of 37%. The procedure consists of a catheter based electrode that stimulates a partially filled bladder for 90 minutes. Success was defined as a reduction in post void residual of 50% in those subjects that were able to void spontaneously, and spontaneous voiding in those with no spontaneous voids (50% of the responders had no spontaneous voids, or voided volume of <50cc per void [28]. Others have concluded this technique is labor intensive and did not alter the voiding program in the majority of subjects [29]. Epididymoorchitis and UTI were common side effects of this therapy [28]. This technique has been compared with sacral neuromodulation previously. This retrospective review was not randomized, but the authors report that all subjects who initially responded to IVES also responded favorably to 4 weeks of S3 sacral nerve stimulation, with a 50% reduction in catheterizing and post void residual volume [28]. Overall this venerable therapy may enjoy resurgence in popularity if improvements in technique and selection criteria can reduce the labor and time involved, as well as improve success rates. One might imagine a more prominent role for IVES if it can be administered in the home or used as a predictor for success with sacral neuromodulation.

Posterior Tibial Nerve Stimulation

Level 1 evidence exists supporting the efficacy of posterior tibial nerve stimulation (PTNS) in patients with non-neurogenic voiding dysfunction, but data on use in neurogenic voiding dysfunction is sparse. The most rigorous non-neurogenic data comes from the Sumit trial. This was a randomized, well powered trial that the authors state was the first sham-controlled neuromodulation trial for overactive bladder [30]. It excluded patients with

neurogenic diagnoses, but demonstrated efficacy for this therapy in 220 patients, with those in the PTNS arm exhibiting a 54.5% response vs. 20.9% for sham treatment [30].

There are also some retrospective series that describe the efficacy PTNS for neurogenic voiding dysfunction that bear mentioning. PTNS was found to improve urinary frequency in multiple sclerosis (MS) from 9 voids per day to 6 voids per day. Nocturia decreased from 3 to 1 episode per night, and post void residual from 98cc to 45cc. 89% of subjects reported "treatment satisfaction of 70%". Quality of life was improved in most domains assessed immediately after 12 weeks of PTNS therapy [31]. Other investigators examining the role of PTNS in MS noted an increase bladder capacity before uninhibited contractions were seen from 124cc to 217cc. Maximum capacity increased from 199cc to 266cc [32]. Investigators from Turkey have studied PTNS and its effect on urodynamic parameters in subjects afflicted with Parkinson's disease as well. Urodynamic studies were performed on 32 subjects before and during active PTNS therapy. The PTNS group demonstrated an increase in cystometric filling volume prior to the first detrusor overactivity episode (145cc to 244cc), as well as an improved bladder capacity (204cc to 301cc) [33].

Some authors have described a similar technique not involving needles called TransCutaneous Posterior Tibial nerve stimulation (TPTNS) used for Multiple Sclerosis with 82% of 70 subjects reporting "improvement of OAB" at 30 days and 83% at 90 days. The subjects underwent daily 20 minute sessions at home. The endpoint was the absence of all of the following: >8 voids per day, >1 nocturia episode, and >3 urinary incontinence episodes weekly [34]. Although the endpoint is not a traditional one, this therapy can be applied daily at home and has results that equal that of more invasive and expensive therapies, such as sacral neuromodulation. This technology merits more investigation.

Hemilaminectomy And Ventral Root Microanastomosis, The Xiao Procedure

Xiao and colleagues garnered significant attention after describing their work rerouting lumbar to sacral nerve roots allowing patients with spinal cord injury to increase bladder capacity and stimulate voiding by merely scratching a dermatome over the appropriate area [35]. Later this was done in 20 patients with myelomeningocele, with 85% gaining "satisfactory bladder control and continence within 8 to 12 months" [36]. This procedure has been reproduced in the US with patients having neurogenic bladder secondary to myelomeningocele. 7 of 9 subjects noted improved storage and volitional voiding by scratching a dermatome. 2 patients were able to stop catheterizing and no patient was able to achieve complete urinary continence. Unfortunately 89% had some degree of muscle weakness, and one demonstrated persistent foot drop at 12 months' follow up [37]. This innovative technique appears reproduceable with modest success outside of the originating institution. The foot drop, initially seen in 25% of subjects in the early Chinese experience has been reduced to 5% in the more contemporary Chinese series by taking less of the L5 nerve root. The remarkable success rate noted by the Chinese investigators (85%) was not quite as good in the US series. The significant risk and morbidity must be weighed against that of comparable options for these patients who fail conventional management such as clean intermittent self catheterization, anticholinergics, botox, and sacral neuromodulation. After these options are exhausted, bladder augmentation, continent catheterizeable channel,

and possibly sling are often considered. These carry significant morbidity as well. This innovative therapy will likely remain available only under investigative protocols until other investigators replicate these results, perhaps in Europe.

Cutaneous Neuromodulation (TENS)

Transcutaneous electrical nerve stimulation (TENS) is attractive because it can be applied directly to the skin at the patient's home and has few adverse side effects. The reuseable nature of the generator makes it cost effective over the long term as well. There are reports of TENS being used for neurogenic voiding dysfunction secondary to myelomeningocele with 9/12 children having improvement on the urinary incontinence score [38]. With regard to non-neurogenic voiding dysfunction, TENS has been used successfully in 42 patients, 50% success at average follow up of 21 months. Following 12 weeks of TENS treatment, mean number of voids per 24 h decreased significantly from 15 to 11 ($p < 0.001$) and mean voided volume increased significantly from 160 to 230 mL ($p < 0.001$). In addition, TENS completely restored continence in 7 (39 %) of the 18 incontinent patients. Before TENS, all 42 patients were dissatisfied or very dissatisfied; following 12 weeks of TENS treatment, 21 (50 %) patients felt satisfied or very satisfied ($p < 0.001$). No adverse events related to TENS were noted. The durability of this therapy, after stimulation treatments have ceased, may be poor [39].

With respect to the non-neurogenic literature, TENS has been used in children without neurologic disorders with mixed results. Investigators from Iowa noted 2/15 (13%) becoming dry and 9/15 (60%) improving. The patients were treated for a mean of 8 months duration and followed for a mean of 13 months. The authors concluded that this therapy is safe and warrants more study [40].

In contrast to the findings from the Iowa group, investigators from Brazil found that para-sacral TENS was more effective than PTNS in 59 children with voiding dysfunction, noting 70% of children in the TENS group exhibited some improvement compared with 9% in the PTNS group. All children with neurogenic causes for voiding dysfunction were excluded, however [41].

Brindley Finetech Stimulator

Introduced in 1978, this therapy for patients with neurogenic voiding dysfunction secondary to complete spinal cord injury has enjoyed moderate success at a limited number of centers. The continence comes from the surgical rhizotomy of the dorsal root of the sacral nerves and the ability to void comes from stimulation of the afferent anterior roots of S2, S3, and S4 using a surgically implanted cuff electrode. The most recent report was from the Netherlands and when compared with matched spinal cord injured controls, 53% of the 46 patients who responded reported urinary continence, compared with 14% of 28 patients who did not undergo the procedure. Interestingly, 37% of those with the stimulator reported they no longer used it for volitional voiding, but 33% of them still enjoyed improved continence secondary to the rhizotomy. The UTI rate for the Brindley stimulator group was 50% (at least 1 per year) compared with 64% for the controls, 86% of whom were managed with

CIC. Those still using it reported significantly higher quality of life scores (Qualiveen) [42] ●. MRI has been safely used in spinal cord injury patients who have undergone this therapy but one device began to malfunction and had to be explanted [43].

Rhizotomy Of The Sacral Nerve Roots

As a permanent alternative to botox administration in the bladder, sacral rhizotomy using RF energy is a minimally invasive technique that targets S2-S4 nerve roots that has not seen widespread use. This technique was described as early as 1978 by Mulcahy and colleagues [44]. Similar techniques have been used to lesion spinal nerves in the treatment of chronic pain [45]. The goal is to lesion the nerve root non-selectively with thermal energy and eliminate detrusor overactivity, but weakening the urinary sphincter can also occur. Loss of reflex erections and ejaculation can also occur with lesioning the parasympathetic nervous system in this way. Recently Cho and colleagues described their experience in 12 spinal cord injured patients who failed conservative measures for treating urinary urge incontinence. They performed urodynamics 1 week before, 1 week after, 4 weeks after the procedure. The mean maximal bladder capacity increased from 292 to 383 ml ($p<0.05$) and mean 24 h incontinent urine volume decreased from 255 to 65 ml ($p<0.05$). The authors report all patients were able to postpone micturition or catheterizing for a longer period of time following RF rhizotomy, and urinary incontinence improved in 11/12 cases [46] ●. In the era of botox this irreversible therapy with more permanent side effects may have a place in those not wanting repeat procedures every 6–9 months, as is necessary for patients treated with botox. The therapy can be repeated and is minimally invasive.

Conclusion

Although sacral neuromodulation dominates the literature, other therapeutic options have proven to be effective for the patient with neurogenic bladder. Exciting areas for future work include neuromodulation utilizing closed loop feedback and neurologic remodeling after neuromodulation.

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