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The role of electrical stimulation in the management of lower urinary track dysfunction following spinal cord lesions

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Abstract

Spinal cord lesions are traumatic or non-traumatic. Spinal cord injuries (SCI) may be complete or incomplete and lead to lower urinary track dysfunction (LUTD) in 95%. Multiple sclerosis is the most frequent cause of non-traumatic spinal cord lesions and leads to LUTD in more than 90% of patients 10 years after diagnosis. LUTD usually presents as neurogenic detrusor overactivity and/or detrusor-sphincter dyssynergia where oral medication is considered to be the first line of treatment and intravesical onabotulinum toxin injections the second, but there are side-effects and refractory cases. In addition, LUTD may present as detrusor underactivity where the above treatment options are not effective.

Clearly there is a need for a third line of treatment. In this review, we discuss the feasibility, safety and efficacy of electrical stimulation for the management of neurogenic LUTD, spanning from historic clinical to recent pre-clinical approaches. Neurostimulation methods are used on complete SCI patients, while neuromodulation methods are mostly used on incomplete spinal lesion patients and can be invasive or non-invasive. There is evidence that neuromodulation inhibits the development of neurogenic LUTD when applied shortly after acute spinal cord lesions. More high-quality studies are needed to prove efficacy of neuromodulation on neurogenic LUTD.

Keywords: Urinary track dysfunction, spinal cord injuries

Introduction

Spinal cord (SC) lesions, traumatic or non-traumatic, bring disastrous consequences upon the patients, who, in addition to motor/sensory impairments, deal with autonomic, sexual, bowel and urinary, disorders. Of the autonomic disorders, the lower urinary track dysfunction (LUTD) poses the most serious threat on health, because of the risk of developing renal failure.

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This risk is considerably lower in patients with slowly progressive nontraumatic neurological disorders, such as multiple sclerosis (MS), compared to spinal cord injury (SCI) or spina bifida[1]. Mortality due to LUTD has decreased in recent decades (3% of SCI deaths), but LUTD still results in symptoms that significantly impact quality of life[2] and patients sometimes even prioritize recovery of LUT function above walking[3,4].

LUTD is reported in an estimated 95% of suprasacral SCI patients and in more than 90% of children with spina bifida. Over 90% of patients suffering from MS for more than 10 years also report LUTD symptoms and urinary incontinence is considered to be one of the worst aspects of the disease[5]. Other causes for SC lesions include SC compression, due to spondylosis, developmental abnormalities or tumors, and ischemia. In this review, we discuss the pathophysiology of LUTD following SC lesions and the applications of electrical stimulation for bladder control, spanning from historic clinical to recent pre-clinical approaches.

There are two functional (and anatomical) units in the LUT: 1) a reservoir (the urinary bladder) and (2) an outlet (bladder neck/internal urethra smooth muscles and external urethra sphincter striated muscle)[6]. A complex neural network controls a reciprocal relationship between the bladder and sphincter function.

During bladder filling, the sympathetic hypogastric nerves (T11-L2) mediate contraction of the smooth (internal) urethral sphincter and inhibition of the detrusor, while the somatic pudendal nerves (S2-S4) mediate contraction of the striated (external) urethral sphincter. This results in low filling and continence pressure[6,7], under the control of the Pontine Continence Center (PCC)[1]. The voiding phase is initiated by a conscious decision, when bladder fullness is perceived, given it is socially appropriate[8]. The Pontine Micturition Center (PMC) is then released from the tonic inhibition of higher centers and the parasympathetic pelvic nerves (S2-S4) mediate detrusor contraction accompanied by relaxation of the pelvic floor and of the outlet, resulting in effective bladder emptying, with no post-void residual (PVR) volume[8]. In health individuals, thinly myelinated Aδ-fibers are responsible for conveying sensations of bladder filling and normally initiate the micturition reflex, triggered by bladder distension, whereas unmyelinated C-fibers, have a greater threshold for activation and are thought to normally remain "silent"[3,6,7]. Spinal cord lesions at cervical or thoracic levels disrupt voluntary control of voiding as well as the normal reflexes that coordinate bladder and sphincter function. Following SCI the bladder is initially areflexic but later becomes hyper-reflexic due to the emergence of a spinal micturition reflex. Studies on animals indicate that LUTD after SCI depends on plasticity of bladder afferent pathways and reorganization of synaptic connections in the SC[6]. Following SC damage, C fibers become mechanosensitive at lower bladder volumes. A segmental spinal reflex then emerges that is mediated by C fiber afferent nerves and results in neurogenic detrusor overactivity (DO).

However, the bladder does not empty efficiently because the detrusor and urethral sphincters contract simultaneously, in a condition termed detrusor-sphincter dyssynergia (DSD), seen in up to 85% of SCI and up to 50% of MS patients[9]. Thus, pressures within the bladder may rise considerably, increasing the risk for vesicoureteral reflux and upper urinary tract damage. These high pressures may even trigger life-threatening dysreflexia episodes on patients suffering from complete SCI above the T7 level[9,10]. Furthermore, DSD results in bladder wall hypertrophy that causes the course of the distal ureter to become progressively perpendicular to the inner surface of the bladder. The vesicoureteral junction consequently becomes incompetent, permitting reflux of urine[3,8]. Injury to the conus medullaris, cauda equina, or peripheral nerves results in poor detrusor contractions, termed neurogenic detrusor underactivity (DU) leading to bladder distension, to the point of overflow incontinence.

Neurogenic LUTD can be managed by intermittent catheterization (IC) if proper bladder emptying is impaired. In case of neurogenic DO and/or DSD, oral medications, mostly anticholinergics, are considered to be the first line of treatment, but, because of side effects, only 30% of the patients continue to take the drug one year after initiation, although they have seen some benefit[9]. Intravesical onabotulinum toxin injections is considered to be the second line of treatment, but there are complications, mostly due to the invasive nature of the procedure. Finally, there are some surgical procedures for carefully selected neurological patients that have high complication and morbidity rates[11]. Clearly

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there is a need for a third line of treatment for refractory neurogenic LUTD. Electrical stimulation could be an option. Safety and efficacy of some methods of electrical stimulation have already been proved on non-neurological LUTD patients and could be used to manage different kinds of neurogenic LUTD as well, even though most of them remain off-label, due to the lack of high-quality studies.

After searching Pubmed and Scopus for relevant articles written in English and checking for duplicates, all identified abstracts were imported into Mendeley bibliography management software. The reference lists of included studies and relevant review articles were additionally searched. (Figure 1: Bibliography flowchart)

Discussion

There are different methods of managing neurogenic LUTD by electrical stimulation. Electrical neurostimulation is the typical, direct stimulation of a neuron with an immediate activating effect on the aimed organ and is usually used on complete SCI patients. On the other hand, electrical neuromodulation (NM) is the indirect stimulation that influences, in other words modulates, pre-existing activity in neural pathways. We therefore stimulate a neuron which affects the function of subsequent neurons to inhibit or activate the aimed organ. NM is usually used on non-traumatic spinal cord lesions or on incomplete SCI patients. Mechanisms of action are debatable. Finally, the direct electrical stimulation of neurons with high-frequency currents is used in order to block them from propagating an undesired action potential. Some of these methods are clinically used on patients already for many years, but others have been used experimentally on humans or animals only.

Electrical Neurostimulation

The idea of direct electrical neurostimulation of the LUT came from Functional Electric Stimulation (FES) of denervated skeletal muscles.

Sacral anterior root stimulation (SARS): SARS was developed by Brindley, 40 years ago, to restore urinary and bowel functions of SCI individuals. Stimulation electrodes were surgically disposed on S2 to S5 sacral anterior roots, following laminectomy, in order to induce detrusor contraction and promote effective (on demand) micturition[12]. SARS at different stimulation settings also may enable defecation and erections. Electrical stimuli are evoked by radiofrequency waves from an external stimulator[11]. Mostly used to restore LUT function, SARS implantation is coupled with sacral differentiation (sectioning of the S2-S5 dorsal roots, a procedure called rhizotomy), to prevent high-pressure DO, and, consequently, promote bladder compliance and prevent incontinence[12,13]. Posterior S2-S5 rhizotomy also reduced the, LUT mediated, autonomic dysreflexia episodes[11] from 43% to 3%[12]. Unfortunately, rhizotomy also results in the potentially irreversible loss of spared perineal sensation and function, thus SARS is not performed on patients with MS or incomplete SCI[12].

SARS simultaneously evokes contraction of the urethral sphincter, resulting in emptying the bladder inadequately[11]. Smooth muscles of the bladder relax more slowly than striated muscles of the urethral sphincter. If intermittent stimulation periods are applied, the urethral muscles will relax but the bladder smooth muscles will keep on contracting, which results in post-stimulus voiding with an intermittent flow pattern of micturition during the stimulation-free intervals[11,12]. Long term usage of SARS results in increased bladder capacity and compliance, decreased intravesical pressure and quality of life improvement. The implants have been successfully tested with 1.5 Tesla MRI[12]. Despite promising results, a decline in implantations was observed. Apart from the required expertise to do this surgery, this decline can be linked to the complication rate (mostly device failures), as well as to the development of mini-invasive alternatives, such as botulinum toxin injections[11]. Furthermore, some patients prefer to wait for a new solution (spinal cord stimulation, stem-cell therapy, neuroprosthesis etc), while others ideologically reject the implantation of electronic devices[12].

Intravesical electrical stimulation (IVES): Katona et al, on 1975[14] was the first to treat 420 patients with transurethral, intravesical electrotherapy in order to improve the function of their "paralyzed" urinary bladders ("2nd-neuron damage"), by reactivation of the intramural bladder receptors. Normal conscious micturition control was obtained by 314 patients. Eb-

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ner et al, on 1992[15] experimentally confirmed on animals that IVES involved a direct activation of bladder mechanoreceptor Aδ afferents, while optimal stimulation frequency was 20 Hz.

Direct bladder wall stimulation (DBWS): Starting in 1958, DBWS was developed, again, for complete SC lesions resulting in a decentralized areflexic bladder, by direct stimulation of viable post-ganglionic nerves located in the bladder wall. The electrodes are placed invasively and optimal stimulation frequency is 40 Hz[16]. When performed on incomplete sacral SC lesion animals it results in pain and strong skeletal muscle contractions[16]. Since Merrill first used the "Mentor" stimulator on 1975, the increasing use of intermittent catheterization for the management of neurogenic DU, made DBWS, as well as IVES, less interesting for clinicians. Nevertheless, efforts are still made for non-migrating electrodes that induce adequate detrusor contractions without any concomitant abdominal wall, leg or anal sphincter contractions[16].

Pelvic nerve stimulation: Pelvic nerve stimulation produced bladder contractions in dogs, but also resulted in co-activation of urethral sphincters. Although it requires lower amplitudes of stimulation than DBWS, application in humans is limited due to the difficulty of electrode placement[10].

Spinal cord stimulation (SCS): It was observed that SCS improved neurogenic DO. A sensory rhizotomy is not required. Most of the studies involved incomplete SCI subjects. Stimulation parameters that have been configured for storage may not be effective for voiding[2]. SCS primarily involved lead placement over the epidural space to manage refractory neuropathic pain. There are commercially available systems that employ epidural SCS to treat chronic neuropathic pain (Abbott, Boston Scientific, Medtronic, Nevro) that are FDA-approved. Permanent electrodes are placed surgically via a laminotomy, only after a successful test period of percutaneous stimulation[17].

Herrity et al[18] found that epidural SCS, with a stimulation frequency of 30Hz, on 5 complete SCI patients, increased efficiency of reflexive voiding from 0-5% to 10-70%. Nevertheless, improvement of LUTD after epidural SCS could be the result of the accompanying step training, since there is an interaction of spinal networks that control bladder and hind limb locomotor function[2]. Havton et al[19] experimentally demonstrated that non-invasive Transcutaneous Spinal Cord Stimulation (TSCS) over the thoracolumbar spine of neurologically intact rhesus macaques can activate the bladder detrusor muscle, the urethral sphincter and pelvic floor muscles. Havton et al suggested that TSCS could augment LUT function if applied on SCI humans as well. The placement of the transcutaneous electrodes is not fixed, since vertebral level of the tip of the conus medullaris varies extensively between humans. This provides an obvious advantage of the non-invasive transcutaneous approach in comparison to the epidural approach. Intraspinal and trans-spinal SCS approaches have also been examined in animal models of SCI[2]. SCS, in general, activates both afferent and efferent pathways. Thus, apart from the direct effect of SCS resulting in effective micturition, there seems to be a neuromodulation effect as well.

Interferential medium frequency current electrical stimulation (IMFC-ES): IMFC ES is a non-invasive approach for the treatment of LUTD first reported in 1985 by Dougall. The interaction of the medium frequencies, inside the body, produces a low frequency field which stimulates the urinary structures, without any significant adverse reactions. IMFC-ES is applied on pubic and abdominal areas immediately after IC, to prevent voiding during stimulation. Daia et al[20] used IMFC-ES on 332 patients shortly after SCI diagnosed, with neurogenic LUTD. IMFC-ES was effective in patients with AIS B/C SCI, since it significantly decreased PVR and incontinence compared with standard care. Patients that exhibit preserved bladder sensitivity were the best beneficiaries. Intentional control of voiding was completely regained by 37 patients after IMFC-ES and only by 13 patients from the control group. This certain study did not allow discriminating between the spontaneous recovery from the spinal shock and the IMFC-ES effect. At 0-5Hz, the IMFC-ES causes innervated skeletal muscles to contract and 5-10Hz may further cause contraction of denervated skeletal muscles. At 11-35Hz, smooth muscles are stimulated and furthermore, 3680Hz can also activate denervated smooth muscles. At 80-100Hz, it relaxes both smooth and skeletal muscles. Thus, IMFC-ES may improve the neural muscular control in neurogenic LUTD in various ways[20].

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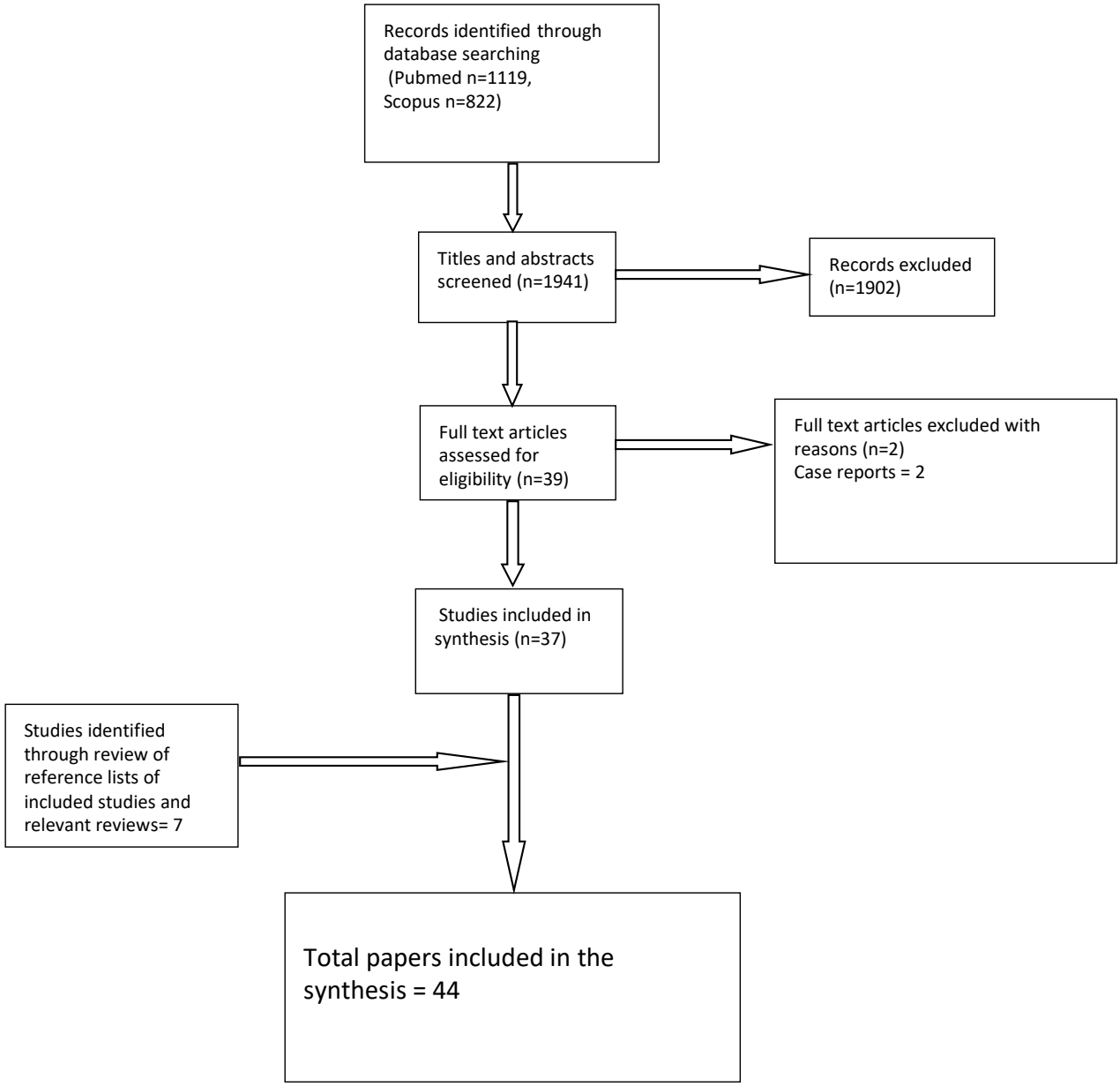

Figure 1. *Flowchart of the study.*

Electrical Neuromodulation (NM)

Neuromodulation is mostly applied on incomplete SC lesions, non-invasively or invasively. Permanently implanted neuromodulation devices are not commonly used on MS patients because of the need for frequent MRIs, since heating of hardware may occur. Most systems are compatible with 1.5Tesla closed magnetic field brain MRIs of specific parameters for no longer than 30 minutes, while the stimulator is turned off [21].

NM was initially used for the treatment of already existing LUT symptoms on non-neurogenic and then on neurogenic patients. We will discuss electrical NM on patients with SC lesions, but since the quality of studies on NM treatment of neurogenic LUTD is not

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satisfactory, it is necessary to take some of the RCTs investigating NM of non-neurogenic LUTD patients under consideration. The main outcome may be indicated by different parameters in different studies, such as urinary frequency, number of leakage episodes, or the score of a questionnaire. The most used definition of success after a certain method of therapy is a >50% reduction in the most important symptom[22]. It was later suggested that application of electrical neuromodulation during the acute phase of SC lesions, mostly SCI, could prevent the development of pathologic reflexes before they lead to OD/DSD. Researchers believe that stimulation of the peripheral sensory afferent fibers blocks the abnormal C-fiber afferent signals from the bladder or inhibits the sensitization of normally "silent" C-fibers [23].

Someone might hypothesize that early NM could also affect the pathological deep tendon reflexes, clonus and spasticity, but this is not the case. It seems that NM protocols do not affect the somatic motoneurons, but only affect bladder innervation[23] and probably other autonomic innervation, such as of the bowel.

NM BY electrical sacral neuromodulation (SNM): SNM involves stimulating the sacral nerves to inhibit DO and was first applied by Tanagho and Schmidt in the 80s[24,25]. Low frequency (10-20Hz) stimulation of S3, with pulse widths between 180 and 210 μs, has been associated with therapeutic success in 43-85%, by modulation of micturition reflexes through stimulation of somatic afferents of the LUT[21,22,25-27]. If a trial stimulation is effective, then a permanent stimulator is implanted (InterStim by Metronic). SNM is an option for symptom control in patients with neurogenic LUTD, who are at low risk of upper urinary tract deterioration. Most of the evidence is focused on incomplete SCI and MS. ASIA D/E SCI patients with preserved bladder filling sensation had higher success rates [21]. Relative contraindications include severe or rapidly progressive neurologic disease, complete SCI, abnormal sacral anatomy or anticipated frequent need for MRI below the head [21]. SNM is not recommended for kids, pregnant women or MS patients with detrusor underactivity[17]. Side effects include stimulation-related pain and hardware infection or malfunction.

Amundsen et al[28] investigated whether botulinum toxin injections are superior to SNM in controlling refractory episodes of urgency/urinary incontinence among 381 non-neurogenic women. Women intravesicaly injected with 200μ of Botox showed small but statistically significant superiority in incontinence episodes reduction (-3.9 vs -3.3 episodes per day), but also showed a higher risk of urinary tract infections (35% vs 11%) probably due to a higher need for transient self-catheterizations. New improved devices are developed, but studies still have a short follow-up. The Axonics® r-SNM System is a novel miniaturized rechargeable SNM device that can deliver therapy for at least 15 years[22]. Sievert et al[29] showed that early implantation of bilateral sacral nerve modulators (SNMs) in 10 complete SCI patients, during the acute bladder-areflexia phase, prevented the development of neurogenic DO. After a mean follow-up of 26 months there was normal bladder capacity, no urinary incontinence, reduced UTI rates, and improved bowel and erectile functionality without nerve damage. They suggested that even earlier SNM could result in more benefits and proposed future fMRI studies in order to prove whether neuronal information is passed through the sympathetic trunk ganglion to the brain even with complete SCI.

NM BY electrical tibial nerve stimulation (TNS): The (posterior) tibial nerve (L5-S3) is a mixed branch of the sciatic nerve that runs superficially behind the lower shin bone medially, making it an easy target for electrical NM. McGuire et al[30], in 1983, were the first to apply TNS on 15 SCI patients with DO, who showed a symptom improvement of 87%. Pulse width is usually 200μs and frequency is low (5-20Hz)[31] and can be delivered by any Transcutaneous Electrical Nerve Stimulation (T.E.N.S.) device. Sessions usually last 30min each and current intensity is as high as the patient feels comfortable with, but not higher than the intensity that results in flexion of the big toe or fanning of the toes. There are no commonly accepted parameters [32].

Transcutaneous TNS (TTNS) is delivered by adhesive skin electrodes, non-invasively, at home, even by the patient or a caregiver, for at least 3 times every week. The active (red) electrode is placed behind the (right) medial malleolus and the ground (black) approximately 10cm higher.[31] Chen et al[33] performed a RCT involving 100 SCI patients with NDO and proved that 4 weeks of TTNS is as effective as solifenacin. Fur-

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thermore, TTNS had no adverse effects. De Seze et al[34] found that 20 minutes of TTNS every day for 3 months reduced urinary urgency, frequency and incontinence on a sample of 70 MS patients. The results lasted for the entire day. Frequency of TTNS usually is 10Hz and intensity is high due to high electrical resistance of the skin.

In the 90s, Stoller was the first to apply Percutaneous TNS (PTNS), that is minimally invasive but more efficient than TTNS.[24,25,32,35] PTNS is delivered by the insertion of a 34G needle active electrode near the tibial nerve (4-5cm cephalad to the medial malleolus) and the ground adhesive electrode is usually placed on the plantar arch. Usually, frequency of PTNS is 20Hz and intensity is only up to 10mA.[24,31] 12 weekly sessions of PTNS seems to be the most effective, while practical as well, protocol.[24,25] Finazzi et al[36] showed that PTNS results in neuroplastic changes of the brain cortex. The efficacy of PTNS at the management of non-neurogenic DO is well established and comparable to anticholinergics.[25,37,38] Tudor et al. conducted a study to compare the results of PTNS in 25 idiopathic and 49 neurogenic (mostly MS:19) patients with DO. No significant differences in outcomes were found. MS patients had a higher probability to require maintenance treatment.[22] Kabay et al[39] found that 12 weeks of PTNS (once every week) on 19 MS patients with NDO resulted in increased bladder capacity and decreased detrusor contractions. More studies are needed to prove efficacy of PTNS on neurogenic LUTD. PTNS is not recommended for MS patients with detrusor underactivity[17].

To overcome the disadvantages of TTNS and PTNS, permanently implanted devices have been developed. "Urgent-SQ" was the first such stimulator used in 2006 and nowadays remotely controlled and charged devices (RENOVA iStim) are implanted, showing good efficacy on idiopathic DO[31]. Stampas et al[23] suggested that neuromodulation via the tibial nerve could also prevent the development of LUTD on acute phase SCI patients. In a randomized control pilot study they showed similar results after 2 weeks of TTNS on complete or incomplete SCI patients with a neurologic level of injury above T10 in order to avoid the possibility of coexisting damage of the detrusor's lower motor neuron. Improved efficacy was found when TTNS achieved toe flexion[23]. TASCI is a RCT that started on 2019 to investigate the same potential of acute phase TTNS on 114 SCI patients. It is planned to be completed on 2024 and also aims to clarify the mechanism behind early NM[4].

NM BY electrical pudental nerve stimulation (PNS): Animal studies have shown that neurogenic DO is inhibited even with complete SCI, by PNS but not by TNS. Thus, it is believed that PNS modulates sacral reflexes while TNS modulates higher suprasacral reflexes that may even be cortically integrated[25].

Peters et al[40] compared PNS to SNM for non-neurogenic LUTD and found symptoms improved in 63% versus 46% respectively. Even surgical procedure is easier for PNS. Nevertheless, it is still not preferred clinically, probably due to lack of good studies to confirm PNS superiority[25]. Liao et al[41] implanted electrodes in order to stimulate the pudendal nerves of 3 dogs the next day after completely dissecting their SC, while 3 more SCI dogs served as the control group. Stimulation frequency was low (5Hz) and resulted in preservation of high bladder capacity and compliance with no contractions after 1 and 3 months. Furthermore, histological examination of their bladders showed that there was no fibrosis, which is thought to be responsible for irreversible deterioration of bladder capacity and compliance and for pressure elevation. This offers an explanation why early neuromodulation has better results than chronic-phase neuromodulation does.

NM BY electrical dorsal genital nerve stimulation (DGNS): The dorsal genital nerve (penile or clitoral) is a sensory branch of the pudendal nerve that is easily stimulated, transcutaneously or percutaneously in order to inhibit DO. Efficient DGNS is confirmed by concomitant reflex contraction of the external anal sphincter[25]. Danish researchers showed that DGNS can acutely suppress unwanted detrusor contractions on SCI[42] and MS[43] patients with DO. DGNS was delivered every time intravesical pressure raised by 10cm-H2O. Unfortunately, the method used to detect this rise could not be clinically applied.

NM BY electrical spinal cord stimulation (SCS): There are studies suggesting that SCS is a viable method for modulating the function of the LUT in human SCI participants, through unclear mechanisms[2]. It is hypothesized that SCS increases the excitability of the

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spinal reflexes necessary for proper LUT function[18].

NM BY electrical perineal nerve stimulation (PeNS): Krhut et al[35] recently proposed a new method of low voltage transcutaneous stimulation of the common peroneal nerve (L4-S2), delivered by the "URIS" device, while a biofeedback foot sensor detects the optimal point for stimulation behind the head of the fibula[35].

Other electrical NM methods: Perineal electrical stimulation (mainly of S3 dermatome) improves DO, but has limited clinical use because of the difficulty in applying the electrodes[23].

In the past, NM methods involving intravesical, anal and vaginal electrical stimulation proved to be inconvenient and ineffective[17].

High-frequency electrical stimulation (HF BLOCK)

High-frequency (10KHz) stimulation can block neurons that would convey a signal with unwanted results. However, although kilohertz frequency nerve block does not produce acute nerve damage, safety and durability of chronic high frequency nerve block remain to be determined.[10]

High-frequency spinal cord stimulation (HF-SCS): Epidural HF-SCS of the dorsal columns was initially used for refractory neuropathic pain management.[11] Schieferdecker et al[44] used HF-SCS on five patients with SCI or MS, resulting in improvement of LUTD and of quality of life; however larger studies are needed for safer conclusions.

High-frequency pudental nerve stimulation (HF-PNS): HF block of the pudendal nerve can inhibit the external sphincter from contracting, in an effort towards efficient low-pressure micturition with minimum PVR. The procedure is invasive and experimental.[11]

In conclusion, it appears that it is only a matter of time before research and technological advances lead to safe, feasible and efficient electrical stimulation methods for managing, or even avoiding the development of, the disfunction of the LUT on neurogenic patients.

New stimulation strategies are currently studied experimentally, mostly on animals and are mainly based on direct spinal cord stimulation or on a combination of spinal root and pudendal nerve stimulation[12].

Conflict of interest

The authors declare no conflicts of interest.

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