Review Article

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Neuroprosthetics for SCI Bladder Management: The Argument for Direct Bladder Stimulation

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Abstract

Implantable neuroprosthetic systems are an important area of practice and research in urinary care for individuals with spinal cord injury (SCI). These devices need to manage three lower urinary tract conditions: urethral sphincter contractions during bladder contractions, an underactive bladder producing poor voiding responses, and neurogenic detrusor overactivity causing urinary incontinence. Two neuroprosthetic approaches have addressed these conditions: sacral anterior root stimulation (SARS) and direct bladder wall stimulation (DBWS). The SARS approach is commercialized for SCI bladder management as the Brindley-Finetech Bladder Control System and is available in Europe. Limitations of this device include invasive surgery and the need for rhizotomy of sacral dorsal (sensory) nerve roots. The DBWS implants produced daily voiding in many SCI individuals, however, clinical use was discontinued primarily because of technical concerns with stimulators and electrodes as well as some cases of poor voiding responses and side effects. These limitations are reviewed as well as efforts to return DBWS to clinical investigations using Permaloc® Systems (Synapse Biomedical Inc., Oberlin OH). This new neuroprosthetic platform includes mapping and intramuscular electrodes as well as multilead cables and new stimulator devices.

Keywords: Spinal cord injury; Urination; Electrical stimulation; Functional electrical stimulation

Neuroprosthetic Approaches

For the spinal cord injured (SCI) individual, urinary management has to address three lower urinary tract conditions: first, detrusor-sphincter-dyssynergia (DSD) or reflex sphincter contractions caused by bladder contractions that prevent voiding; second, an underactive bladder where spontaneous bladder contractions do not continue long enough or with sufficient pressure to produce effective bladder emptying; and, third, neurogenic detrusor overactivity (NDO, where detrusor is the bladder pressure after subtraction of abdominal pressure) were unwanted events occur spontaneously causing urinary incontinence [1-6]. Following SCI, intermittent catheterization in conjunction with anticholinergic medication or botulinum toxin (BT) injection into the bladder wall to manage NDO and urinary incontinence addresses these three conditions and is the most common method of bladder management. Catheters, however, are associated with lower urinary tract morbidity such as urinary tract infections, incontinence, and urethral trauma [1,2].

Two neuroprosthetic approaches have been used as alternatives to intermittent catheterization: sacral anterior root stimulation (SARS) and direct bladder wall stimulation (DBWS) [6-13]. The SARS approach has been commercialized under the name Brindley-Finetech Bladder Control System (FineTech Medical Ltd, Welwyn Garden, UK) in Europe, and Vocare in the United States; however, it is currently only available in Europe [6-13]. Limitations of this device; however, include invasive surgery and the need for rhizotomies of sacral dorsal (sensory) nerve roots. This approach has been extensively reviewed; therefore, only recent developments to address outstanding limitations are discussed. The DBWS approach has demonstrated daily voiding in many SCI individuals; however, clinical studies were discontinued because of concerns with stimulators and electrodes in some patients that limited voiding or caused side effects such as increased urethral resistance or pain [8,9]. Recent developments for both neuroprosthetic approaches to address identified limitations are reviewed. Developments for DBWS are discussed in detail including work by Synapse Biomedical Inc. (Oberlin, OH) to bring Permaloc® Systems to clinical investigations.

Sacral Anterior Root Stimulation

Brindley-finetech bladder control system

The Brindley-Finetech SARS device uses an implanted stimulator and tripolar cuff electrodes to stimulate the second to fourth anterior sacral nerve roots as well as a dorsal afferent rhizotomy of the same sacral roots [7-13]. The anterior nerve roots that are stimulated include fibers innervating the skeletal urethral sphincter and the bladder; thus, voiding is prevented during stimulation induced bladder contractions due to urethral sphincter contractions. Only post-stimulation voiding is produced and this method relies on longer bladder contractions after the end of stimulation periods than for urethral skeletal sphincter muscle. Multiple stimulation periods are needed with peak bladder pressures of 50 cm H_2O required for complete voiding [7]. Voiding responses with the Brindley-Finetech SARS can vary; for example, we reported that two SCI individuals

implanted with this system had voiding problems [12]. The first individual could not void with a standard 24 Hz stimulation frequency; however, 35 Hz was found to be effective. The second individual had a urethral sphincterotomy (unannounced) prior to his implant and could not void with stimulation in the sitting position; this was resolved by using a donut shaped seat cushion. A recent review of the Brindley-Finetech device outcomes stated that a large majority of SCI individuals obtained daily voiding that was catheter, incontinence, and infection free as well as improved patient quality of life [7,11,13].

There are two primary areas of limitations for the Brindley-Finetech SARS device. The first area is with invasive surgical procedures including two spinal laminectomies: the first bone removal is over the lower lumbar vertebra to gain access for the sacral sensory nerve roots and the second bone removal is over the sacrum to implant bilateral electrodes on second to fourth anterior sacral nerve roots [11]. The second limitation is with the sacral nerve afferent rhizotomy which causes a loss of spinal reflexes to pelvic organs including the bladder, bowel, and sexual organs [7]. The loss of bladder reflexes is managed with a post stimulation voiding program; bowel evacuation is also facilitated by simulation. The loss of erectile activity has been more difficult to restore [7]; for example, at our institution where two SCI individuals were implanted with this device, both complained about loss of erectile function [11]. In summary, the limitations identified for the Brindley-Finetech SARS System have fostered extensive new research to address the concerns.

Invasive procedures for SARS vertebral laminectomies are hard to avoid because access to the sacral nerves within the sacral canal are needed. In addition, avoiding the sacral afferent neurectomy is also difficult because it is important for post-stimulation voiding in two ways. First, neurectomy prevents sphincter contractions that can occur after each stimulation period due to sensory activation during the stimulation period. We conducted studies that identified this problem in four chronic SCI felines with intact sacral nerves; studies were conducted during terminal procedures under anesthesia, and compared SARS and DBWS with implanted electrodes [14]. For the first test, equivalent stimulating parameters were used for both methods; but, there was a urethral catheter to record bladder pressure which prevented voiding. Both SARS and DBWS induced similar high peak bladder pressures. The catheter was then removed and the same stimulation induced robust voiding with DBWS both during and after stimulation whereas SARS only induced a small amount of voiding after stimulation. Subsequent tests investigated the causes of poor voiding responses to SARS with intact sacral nerves. Recordings of urethral electromyography and pressure after stimulation demonstrated that sphincter contractions occured and these contractions were not present with DBWS. Adverse urethral effects of SARS after stimulation with intact sacral nerves should not be unexpected as it is well known that for SCI individuals even slight sensory stimulation below the level of the lesion can cause prolonged leg spasms. Therefore, with conditions of SARS and intact sacral sensory nerves, the large amounts of sensory activation occurring during stimulation can be expected to cause ongoing sphincter reflexes and spasms after stimulation.

The second way that sacral afferent neurectomy assists with post-stimulation voiding is by preventing DSD [7,11]. This adverse bladder reflex caused urethral sphincter contractions that are prevented by the rhizotomy. It should also be mentioned that the sensory lesion also managas NDO and urinary incontinence [7,11]. In summary, access to

the sacral nerve roots is needed for SARS making it difficult to avoid invasive surgical procedure and the sacral afferent rhizotomy has multiple benefits for SARS.

New SARS methods: One new SARS method that has avoided the invasive laminectomies and nerve rhizotomy was conducted by Possover et al. [15]. Laparoscopic methods were used to implant two Brindley-Finetech electrodes on bilateral sacral nerves in the pelvic area near the spine of three SCI participants. Bilateral pudendal nerves also had wire electrodes sutured to them [16-22]. Continuous stimulation of the pudendal nerves at 20 Hz was used to manage NDO and prevent urinary incontinence resulting in bladder filling volumes of 500 ml. This strong bladder inhibition shown by the very large bladder filling volumes was described as 'bladder block,' a novel concept in the area of neuromodulation for SCI. In two of the three individuals, when the 20 Hz pudendal nerve stimulation was turned off, strong spontaneous contractions occurred with effective voiding and small residual volumes. As these patients could not void prior to their implants due to DSD, the pudendal nerve stimulation appeared to provide reduction of the DSD. For the third individual, voiding did not occur when pudendal nerve neuromodulation was stopped at the 500 ml bladder volume. Sacral nerve stimulation was needed to induce bladder contractions and emptying and this was conducted in conjunction with high-frequency (1.2 KHz) stimulation of the pudendal nerves to manage DSD and lower urethral resistance. These novel neuroprosthetic approaches by Possover et al. [15] need further investigation. Possible limitations with this approach include difficult laparoscopic methods and need for implantation of multiple electrodes and stimulators.

Five new methods to avoid the SARS afferent rhizotomy are under development as highlighted by the recent work by Chew et al. [16]. First, stimulation and blocking of separated sacral afferent and efferent nerve roots has potential [7,16]. Second, a unidirectional, tripolar nerve cuff electrode on the pudendal nerve has been proposed [8,17]. Third, high-frequency stimulation for pudendal or sacral nerve blocking [9,16,18-10]; this method is limited by the need for nerve cuff electrodes to be implant on pelvic pudendal nerves that are located deep in the pelvis [21]. Fourth, improved methods of neuromodulation for bladder inhibition and NDO management are being investigated on sacral and pudendal nerves [9,22-25]. And, fifth, botulinum toxin (BT) injections into the urethral skeletal sphincter should be considered; such injections might allow for voiding during stimulation, a condition that would greatly facilitate SARS technology [26]. We also investigated several methods to avoid afferent neurectomy including minimally invasive SARS electrodes implanted in the sacral canal [14,27-30], optimization of sacral nerve stimulation [31], and sacral nerve neuromodulation for NDO and urinary incontinence management [32]. With the exception of work by Possover et al. [15] new SARS techniques have not been extended to clinical studies and technical challenges remain difficult to resolve.

Direct bladder wall stimulation (DBWS)

DSD, NDO management: Management of DSD and NDO following SCI is important for DBWS methods. Detrusor sphincter dyssynergia can be caused by three different uninhibited spinal reflex pathways. The first and primary pathway is an uninhibited reflex between the bladder and the urethral sphincter where bladder contractions result in sphincter contractions. The second is an uninhibited urethral-to-urethral reflex where passage of urine in the urethra causes reflex sphincter contractions. The third pathway involves the sympathetic

nervous system where sensory activity from the bladder or urethra cause reflex sympathetic activity and urethral smooth muscle contractions prevent voiding [1,5,33,34]. A related problem to this sympathetic induced urethral constriction is autonomic dysreflexia where uninhibited sympathetic activity causes increased blood pressure [2,3].

Three classification systems have been used to characterize DSD following SCI. Early classification systems used electromyography whereas more recent criteria have included functional voiding [35]. Characterization of DSD is complicated by the duration and characteristics of bladder contractions that can confound assessment. Classifications have not separated DSD occurring during the initiation of a bladder contraction or changing peak bladder pressure from DSD during a sustained and constant peak bladder pressure. We were able to distinguish DSD based on these different types of bladder contractions in a series of SCI individuals where some exhibited sustained peak bladder pressures [35,36]. Our assessment also included using a dynamic bulbocavernosus reflex (DBC) test. This test periodically elicits bulbocavernosus reflex (BC) by stimulating the dorsal nerve of the penis with surface electrodes once every 4 s and recording peak reflex anal sphincter pressure responses. The anal sphincter was used to mimic the urethral sphincter as there is a close association of these two sphincters following SCI. The DBC test was evaluated during cystometry to provide an independent measure of spinal reflex excitability, an underlying condition of DSD, during a bladder filling and bladder contraction cycle [35,36].

The DBC during cystometry was evaluated in five SCI patients and the baseline anal sphincter pressure increased at the onset of bladder contractions but returned to baseline values during sustained bladder contraction [35]. Severe DSD, therefore, only occurred during the onset of the bladder contraction and occurred during changing peak bladder pressures. These conditions of bladder contractions causing severe DSD is consistent with the understanding that the highest amounts of afferent activity arises from the bladder wall during the period of maximal wall shear when active movement of bladder wall muscles occurs during shortening. In contrast, peak bladder pressures that are sustained and non-fluctuating have reduced wall sheer activity with a corresponding reduced afferent sensory activity [5,35].

The results of the periodic BC responses during the DBC test demonstrate increased responses during bladder filling but the largest BC increases occurr during bladder contractions [35]. A high BC reflex response during sustained portions of bladder contractions indicate that spinal reflexes remain in a heightened state. This heightened state likely produces interrupted voiding pattern that often occur during SCI reflex voiding when the passage of urine in the urethra triggers sphincter contraction and interrupted voiding. This mechanism of DSD has important implications for DBWS where prolonged bladder contractions are induced for evacuation during stimulation which is associated with less DSD [14,37,38]. If DBWS induced voiding occurs at pressures over 50 cm H_2O then DSD is indicated and management of the condition is needed. For skeletal urethral sphincter contractions due to the first two mechanisms of DSD, BT injection into the sphincter should be considered [39,40]. Paralysis of the sphincter with BT has no side effects but does require repeat injection at a six to nine month interval [26,41]. The third neural pathway causing DSD is the sympathetic system resulting in contraction of smooth muscle of the bladder neck preventing voiding. This type of DSD, if shown in video-urodynamic studies, can be managed with alpha-1 receptor blockers or botulinum toxin injections

into the proximal urethra [38]. In addition, Magasi et al. [39,40] used proximal urethral incisions to manage this problem in three patients using DBWS.

We conducted DBC testing in a chronic SCI feline model [35]. In contrast to clinical results, peak BC responses were reduced during bladder contractions showing synergistic effects; however, baseline anal and urethral sphincter pressures were elevated during bladder contractions indicating adverse bladder-sphincter reflexes. We interpreted these results as mixed synergy and dyssynergia of bladder-urethral reflexes for this quadruped model of chronic SCI. Limited DSD in the upper-neuron lesion SCI animal model has been reported; for example, it is ease to empty the bladder using squeeze maneuvers (Crede') [27,28,37,38]. In contrast, squeeze maneuvers produce limited or only high-pressure voiding in SCI patients [1,2,5].

A possible alternative approach to manage DSD would be application of surgical clips to the superficial surface of the skeletal urethral sphincter to produce nerve crush injury (unpublished). Such an approach would need to be developed first in an animal model. Locations for the clips should be at the surgical two and ten o'clock locations near the dorsal neurovascular bundles that include the sphincter innervation, the perineal branch of the pudendal nerve. Effects of such procedures should be long lasting as nerve regrowth past implanted clips would probably not occur. For NDO and urinary incontinence problems that might be associated with DBWS, use of anticholinergic medication or neuromodulation for bladder inhibition should be first line treatment as detailed below [1,2,42].

DBWS studies

Early studies by five investigators demonstrated that DBWS is viable approach for bladder management following SCI. Stenberg et al. [43] included four upper-motor neuron lessoned SCI patients implanted with an Avco-Everett stimulator which had two bipolar sets (four electrodes total) of stainless steel wire electrodes braded into the bladder wall. Three of four patients obtained reflex voiding. Hald et al. [44] implanted the same device in three upper-motor neuron lessoned SCI patients leading to strong bladder contractions in all three patients. A third investigative team, Halverstat et al. [45,46] implanted the Avco-Everett device in eight patients and a MentorR bladder stimulator with bipolar sets of electrodes (total four electrodes) in two patients with peripheral nerve injuries. Daily voiding was obtained in seven; two failures occurred due to lead erosion or detachment and one failure due to pain. Another group, Merrill et al. [47] implanted the Mentor device in five cases; four had peripheral nerve injury and one a complete lower motor neuron injury. Three patients obtained daily voiding whereas two did not. The protocol failed in one subject due to chronic urinary tract infections and in another due to pain during stimulation. The fifth group, Jonas et al. [48] implanted the Mentor device in two patients with upper-motor-neuron SCI and nine subjects with incomplete lower motor neuron injuries. Postoperative follow-up ranged from four months to four years; a bladder neck or sphincterotomy operation was conducted to lower outflow resistance and one patient received an artificial sphincter to prevent incontinence. Voluntary control of voiding returned in seven patients. Three failures were due to poor bladder responses or infection and device rejection.

These early studies of DBWS identified limitations in some patients in the areas of: first, electrodes that were too large reducing the charge injection density needed for stimulating the small-diameter parasympathetic fibers innervating the bladder wall; second, electrodes

that were insufficient in number or had less than optimal implant locations; and third, stimulation may have been conducted at too low of a frequency or with too short of pulse durations. These limitations; however, were partly addressed by Magassi et al., conducting the most recent clinical work for DBWS (1976, 1986) [39,40]. They implanted the Electrical Vesical Stimulator PMS-3 (Physico-Medical Inc, Canada) with eight platinum-iridium disk electrodes on the bladder wall as four bipolar sets in 32 patients. Twenty-one cases had peripheral neural injuries and eleven had central injuries, most of which were localized to the spinal cord. Stimulating current was increased until voiding started and stimulation was continued until the bladder emptied. Repeated stimulations were used until a small residual volume was obtained. Voiding was constricted in three patients with proximal urethral closure which was managed with a bladder neck incision. Voiding was therefore satisfactory in all 32 patients over a one to two year period. Following these promising results, no further studies were conducted as the device became unavailable as the manufacturer went out of business.

Neuroprosthetic systems also need to be developed for SCI individuals with lower motor neuron injuries. This type of injury including the lower lumbar and sacral spinal cord causes lesions to preganglionic nerve fibers innervating the bladder. Thus, SARS methods because they include sacral nerve roots cannot be used for these patients. In contrast, DBWS can be effective for stimulation of the remaining post-ganglionic fibers located on the bladder wall. Several of the prior investigations [39-45] with implants in patients with these types of injuries had positive results. In addition, we conducted chronic studies in chronic lower motor neuron injured SCI felines and demonstrated induction of high bladder pressure and daily voiding [37]. Thus, if DBWS returns to clinical investigations, lower motor injured SCI individual's should be included in the studies.

Propose permaloc® systems: In 1992 we identified advantages of DBWS compared to SARS during terminal procedures in anesthetized chronic spinal felines [14]. Following the studies, we investigated optimal methods of DBWS with Permaloc® or related electrodes. Between 1993 and 1997 woven-eye and suture electrodes were tested on the bladder wall [37,38,49] and in 2005 microstimulators were tested [50]. In 2008 we also tested monopolar Permaloc® Intramuscular electrodes [51]. The above studies were conducted in several different animal models including acute felines and canines with intact spinal cords and chronic SCI felines both with lower and upper motor neuron lesions. In all of these studies, bladder pressures over 40 cm H_2O were induced that were suitable for voiding.

In the most recent study from our laboratory (2012), seven female York-Landrace swine were investigated under anesthesia [51]. Four bipolar Permaloc® electrodes were implanted on the bladder wall as two bilateral sets 1 cm medial and 1 cm rostral to the ureters. Using 40 mA of stimulation, peak bladder pressures of only 10 ± 2 cm H_2O were induced. This limited pressure response to stimulation may have occurred for several reasons: one, because of lack of any spontaneous bladder activity the animals demonstrated no bladder contractile activity when filled to over 500 ml. Two, the stimulating surfaces of the Permaloc® bipolar electrodes were only separated by 5 mm which was too short whereas Magassi et al. used a much wider separation in their bipolar sets [39,40]. Three, there were no mapping electrodes available for better identifying effective electrode implant locations, a limitation that applies to all prior DBWS stimulation studies; four, too few electrodes may have also been used as, for example, Magassi et al., used eight electrodes that functioned separately [39,40]. Future studies

for DBWS with Permaloc® systems being designed to address these concerns are described with developments in six key area [52].

I. Minimally Invasive: laparoscopic methods are currently used for all Permaloc® electrodes and systems [53-55]. In the future, DBWS could be considered for SCI individuals receiving Permaloc® systems in their diaphragm for respiratory management. The implantation laparoscope could be turned caudally for bladder wall mapping, implants, and further testing. If effective stimulation were shown during implantation protocols then they would remain implanted for chronic use.

II. Staged Methods: staged methods for bladder management are part of DBWS programs. Interventions for each of the three lower urinary tract problems following SCI would only be used if they were lower urinary problems that needed to be addressed. For example, individuals who responded to DBWS with complete evacuation at detrusor pressures less than 50 cm H_2O, the same pressure criteria used for SARS methods, would not need to receive treatment for DSD.

III. Permaloc® Systems: Permaloc® electrode systems are being developed for future DBWS applications:

Permaloc® Mapping electrodes (Figure 1A): would be used to determine optimal implantation sites on the bladder wall. The small diameter electrode is inserted with a 19 gauge needle, and could be tested at multiple sites to optimize the location prior to implantation of permanent electrodes. These methods will address concerns raised in prior studies of DBWS where difficulties in optimal placements of electrodes on the bladder wall were identified.

Permaloc® Intramuscular electrodes (Figure 1B): this permanent electrode would be inserted at optimal locations determined with the mapping electrodes. A slight modification to this commercial electrode is to move the polypropylene barb 5 mm distal from the tip exposing the whole length of the helical wire stimulating surface. This modification is important because implantations with the stimulating surface of the electrode as close as possible to bladder nerves is to produce low current activation of the bladder wall [51,52]. The small size of these electrodes is expected to provide high charge injection density to better stimulate the bladder innervation, a limitation sited in prior studies using larger electrodes.

A Permaloc® Multilead-Cable device (Figure 1C): has been designed to connect to five implanted Permaloc® Intramuscular electrodes. This will limit the number of cables crossing the skin to an external stimulator or being tunneled to an implantable stimulator. The connector for this electrodes is FDA approved for chronic human use.

12-channel Permaloc® Laboratory Stimulator: a 12 channel Permaloc® Stimulator-Trainer with isolated, high current, bipolar and biphasic stimulation for bladder wall and pudendal nerve activation is available from Synapse Biomedical Inc. This is a computer controlled device and programs are provided for each stimulation protocol. A small external stimulator that is battery powered is currently used for FDA approved Permaloc® Systems to manage respiration in SCI patients [53,54]. This device is expected to be modified for the proposed bladder application. Implantable stimulators could be developed in the future, if warranted.

IV. Acute Animal Studies: use of an anesthetized canine model is recommended to further investigate some of the DBWS methods. This animal model has been shown to be a good model of the human lower urinary tract conditions [36-38,50-52]. In addition, use of a modern anesthetic regime such as respiratory anesthetic and fentanyl should
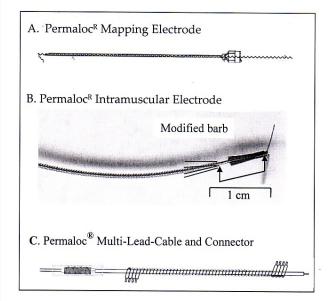
reduce the depression of reflexes common with other anesthetics such as Nembutal.

V. Chronic Animal Studies: Chronic animal studies are expected to be needed to insure that the Permaloc® Intramuscular Electrodes can be secured long-term in the bladder wall and also provide effective long-term stimulation.

VI. Technology Transfer: these processes will depend on resolving remaining limitations with DBWS in animal models. The development of a Class III implantable device clinical trial, or through Orphan Device Program will be needed in the United States for future clinical investigations. Synapse Biomedical, Inc is developing the Permaloc® Systems for DBWS applications, and the costs of obtaining the devices are relatively low compared to the special engineering and manufacturing requirements of providing them.

Figure 1: A. Permaloc® Mapping Electrode proposed to determine optimal stimulation sites on the bladder wall. B. Permaloc® Intramuscular Electrode for chronic implantation. A modification is shown for moving the polypropylene barb 6 mm to expose the entire stainless steel stimulating surface. C. Implantable Permaloc® Multi-Lead-Cable with connectors for connection to five Permaloc® intramuscular electrodes; engineering drawings from Synapse Biomedical, Inc.

Our laboratory has been the only one reporting on DBWS since Magassi et al. [39]; our most recent study was conducted in 2012 [21,52]; thus, it is important that other investigators in the field to also include DBWS protocols. These methods are easy to incorporate into lower urinary tract studies; simple wire hook electrodes can be used; Permaloc® Mapping and Intramuscular electrodes are available from Synapse Biomedical Inc (purchase order). In particular, SARS laboratories should consider DBWS methods as they may provide further insight into advancing neuroprosthetic approaches for SCI bladder management.

The Permaloc® neuroprosthetic platform described here has potential for management of a wide range of paralysis problems encountered for SCI individuals. In the respiratory area, the system is being used for the diaphragm and may be used in the future for accessory muscle pacing. Accessory respiratory muscles, abdominal and upper-thorax, pacing alone has been shown to induce large respiratory responses suitable for cough [55]. Other applications are being considered for this end-organ stimulation approach including bowel, sexual organs, and limb and trunk stability.

Conclusion

Both DBWS and SARS neuroprosthetic systems hold great promise to assist SCI individuals with their lower urinary tract management and without catheterization. Limitations of SARS, however, of invasive surgical procedures and sacral nerve root dorsal rhizotomy remain as significant technical hurdles. In contrast, DBWS approaches include minimally invasive surgery and staged methods. New technology for DBWS include Permaloc® Electrode Systems that are being developed include mapping and intramuscular electrodes as well as multilead-cable devices and stimulators with multiple independent bipolar and biphasic stimulation channels. Further animal urinary incontinence

Acknowledgement

References

1. Hayes KC, Bassett-Spiers K, Das R, Ethans KD, Kagan C, et al. (2007) Research priorities for urological care following spinal cord injury: recommendations of an expert panel. Can J Urol 14: 3416-3423.

2. http://www.pva.org/site/DocServer/Bladder.WEB.pdf?docID=1101

3. Nosseir M, Hinkel A, Pannek J (2007) Clinical usefulness of urodynamic assessment for maintenance of bladder function in patients with spinal cord injury. Neurourol Urodyn 26: 228-233.

4. Linsenmeyer TA (2013) Use of botulinum toxin in individuals with neurogenic detrusor overactivity: state of the art review. J Spinal Cord Med 36: 402-419.

5. Yalla SV, Blunt KJ, Fam BA, Constantinople NL, Gittes RF (1977) Detrusor-urethral sphincter dyssynergia. J Urol 118: 1026-1029.

6. Tanagho EA, Schmidt RA (1988) Electrical stimulation in the clinical management of the neurogenic bladder. J Urol 140: 1331-1339.

7. Martens FM, Heesakkers JP (2011) Clinical results of a brindley procedure: sacral anterior root stimulation in combination with a rhizotomy of the dorsal roots. Adv Urol 2011: 709708.

8. Rijkhoff NJ, Wijkstra H, van Kerrebroeck PE, Debruyne FM (1997) Urinary bladder control by electrical stimulation: review of electrical stimulation techniques in spinal cord injury. Neurourol Urodyn 16: 39-53.

9. van Balken MR, Vergunst H, Bemelmans BL (2004) The use of electrical devices for the treatment of bladder dysfunction: a review of methods. J Urol 172: 846-851.

10. Wenzel BJ, Boggs JW, Gustafson KJ, Grill WM (2006) Closed loop electrical control of urinary continence. J Urol 175: 1559-1563.

11. Brindley GS, Polkey CE, Rushton DN, Cardozo L (1986) Sacral anterior root stimulators for bladder control in paraplegia: the first 50 cases. J Neurol Neurosurg Psychiatry 49: 1104-1114.

12. Walter JS, Wheeler JS Jr, Creasey G, Chintam R, Riedy L, et al. (1998) Optimization of sacral ventral root stimulation following SCI: two case reports with six-month follow-up. J Spinal Cord Med 21: 211-219.

13. Creasey GH, Grill J, Korsten M, Sang H, Betz R, et al. (2001) For the Implanted Neuroprosthesis Research Group. An implantable neuroprosthesis for restoring bladder and bowel control to patients with spinal cord injuries: a multicenter trial. Arch Phys Med Rehabil 82:1512-1519.

14. Walter JS, Sidarous R, Robinson CJ, Wheeler JS, Wurster RD (1992) Comparison of direct bladder and sacral nerve stimulation in spinal cats. J Rehabil Res Dev 29: 13-22.

15. Possover M, Schurch B, Henle KP (2010) New strategies of pelvic nerves stimulation for recovery of pelvic visceral functions and locomotion in paraplegics. Neurourol Urodyn 29: 1433-1438.

16. Chew DJ, Zhu L, Delivopoulos E, Minev IR, Musick KM, et al. (2013) A microchannel neuroprosthesis for bladder control after spinal cord injury in rat. Sci Transl Med 5: 210ra155.

17. Rijkhoff NJ, Wijkstra H, van Kerrebroeck PE, Debruyne FM (1997) Selective detrusor activation by electrical sacral nerve root stimulation in spinal cord injury. J Urol 157: 1504-1508.

18. Ackermann DM Jr, Foldes EL, Bhadra N, Kilgore KL (2009) Effect of bipolar cuff electrode design on block thresholds in high-frequency electrical neural conduction block. IEEE Trans Neural Syst Rehabil Eng 17: 469-477.

19. Boger A, Bhadra N, Gustafson KJ (2008) Bladder voiding by combined high frequency electrical pudendal nerve block and sacral root stimulation. Neurourol Urodyn 27: 435-439.

20. Tai C, Wang J, Wang X, Roppolo JR, de Groat WC (2007) Voiding reflex in chronic spinal cord injured cats induced by stimulating and blocking pudendal nerves. Neurourol Urodyn 26: 879-886.

21. Allen JC, Walter JS, Sayers S, Singh S, Wang W, et al. (2012) Comparison of bipolar lead electrodes for high-frequency blocking of the pudendal nerve. The Internet Journal of Urology 9.

22. Kirkham AP, Shah NC, Knight SL, Shah PJ, Craggs MD (2001) The acute effects of continuous and conditional neuromodulation on the bladder in spinal cord injury. Spinal Cord 39: 420-428.

23. Kirkham AP, Knight SL, Craggs MD, Casey AT, Shah PJ (2002) Neuromodulation through sacral nerve roots 2 to 4 with a Finetech-Brindley sacral posterior and anterior root stimulator. Spinal Cord 40: 272-281.

24. Sievert KD, Amend B, Gakis G, Toomey P, Badke A, et al. (2010) Early sacral neuromodulation prevents urinary incontinence after complete spinal cord injury. Ann Neurol 67: 74-84.

25. Martens FM, Heesakkers JP, Rijkhoff NJ (2011) Surgical access for electrical stimulation of the pudendal and dorsal genital nerves in the overactive bladder: a review. J Urol 186: 798-804.

26. Wheeler JS Jr, Walter JS, Chintam RS, Rao S (1998) Botulinum toxin injections for voiding dysfunction following SCI. J Spinal Cord Med 21: 227-229.

27. Tang PC, Walter JS (1984) Voiding in conscious spinal dogs induced by stimulating sacral and coccygeal roots with the "volume conduction" method. Neurourol Urodyn 3: 43-50.

28. Walter JS, Wheeler JS, Robinson CJ, Bolam MS, Wurster RD (1988) Urodynamic responses to sacral stimulation in the chronic spinal dog. Neurourol Urodyn 7: 13-25.

29. Walter JS, Wheeler JS, Robinson CJ, Khan T, Wurster RD (1989) Urethral responses to sacral stimulation in chronic spinal dog. Am J Physiol 257: R284-291.

30. Walter JS1, Robinson CJ, Khan T, Wheeler JS, Wurster RD (1989) Sacral epidural electrodes for voiding in the chronic spinal dog. Stereotact Funct Neurosurg 53: 113-124.

31. Walter JS, Tang PC, Wheeler JS (1991) Effects of bladder volume on detrusor contractility during sacral nerve stimulation. Neurourol Urodyn 10: 61-69.

32. Walter JS, Wheeler JS, Robinson CJ, Wurster RD (1993) Inhibiting the hyperreflexic bladder with electrical stimulation in a spinal animal model. Neurourol Urodyn 12: 241-252.

33. Rudy DC, Awad SA, Downie JW (1988) External sphincter dyssynergia: an abnormal continence reflex. J Urol 140: 105-110.

34. Linsenmeyer TA, Horton J, Benevento J (2002) Impact of alpha1-blockers in men with spinal cord injury and upper tract stasis. J Spinal Cord Med 25: 124-128.

35. Walter JS, Wheeler JS Jr, Dunn RB (1994) Dynamic bulbocavernosus reflex: dyssynergia evaluation following SCI. J Am Paraplegia Soc 17: 140-145.

36. Walter JS, Wheeler JS, Wurster RD, Sacks J, Dunn R (2003) Preliminary observations of a synergistic bladder-sphincter relationship following spinal cord injury in a quadruped animal. J Spinal Cord Med 26: 372-379.

37. Walter JS, Wheeler JS, Cai W, King WW, Wurster RD (1999) Evaluation of a suture electrode for direct bladder stimulation in a lower motor neuron lesioned animal model. IEEE Transactions on Rehabilitation Engineering 7: 159-166.

38. Walter JS, Wheeler JS, Cai W, Wurster RD (1997) Direct bladder stimulation with suture electrodes promotes voiding in a spinal animal model: a technical report. J Rehabil Res Dev 34: 72-81.

39. Magasi P, Simon Z (1986) Electrical stimulation of the bladder and gravidity. Urol Int 41: 241-245.

40. Magasi P, Novoszel T, Koncz P (1976) Electronic bladder stimulation in spinal cord paralysis. Urol Int 31: 332-342.

41. Perkash I (1996) Contact laser sphincterotomy: further experience and longer follow-up. Spinal Cord 34: 227-233.

42. Horstmann M, Schaefer T, Aguilar Y, Stenzl A, Sievert KD (2006) Neurogenic bladder treatment by doubling the recommended antimuscarinic dosage. Neurourol Urodyn 25: 441-445.

43. Stenberg CC, Burnette HW, Bunts RC (1967) Electrical stimulation of human neurogenic bladders: experience with 4 patients. J Urol 97: 79-84.

44. Hald T, Meier W, Khalili A, Agrawal G, Benton JG, et al. (1967) Clinical experience with a radio-linked bladder stimulator. J Urol 97: 73-78.

45. Halverstadt DB, Parry WL (1975) Electronic stimulation of the human bladder: 9 years later. J Urol 113: 341-344.

46. Merrill DC (1975) Clinical experience with the Mentor bladder stimulator. III. Patients with urinary vesical hypotonia. J Urol 113: 335-337.

47. Jonas U, Hohenfellner R (1978) Late results of bladder stimulation in 11 patients: followup to 4 years. J Urol 120: 565-568.

48. Walter JS, Wheeler JS, Cogan SF, Plishka M, Riedy LW, et al. (1993) Evaluation of direct bladder stimulation with stainless steel woven eye electrodes. J Urol 150: 1990-1996.

49. Walter JS, Fitzgerald MP, Wheeler JS, Orris B, McDonnell A, et al. (2005) Bladder-wall and pelvic-plexus stimulation with model microstimulators: Preliminary Observations. J Rehab Res Dev 42: 251-260.

50. Bresler L, Walter JS, Jahoda A, Wheeler JS, Turk T, et al. (2008) Effective methods of pelvic plexus nerve and bladder stimulation in anesthetized animal model. J Rehabil Res Dev 45: 627-637.

51. Walter JS, Allen JC, Sayers S, Singh S, Cera L, et al. (2012) Evaluation of bipolar Permaloc® electrodes for direct bladder stimulation. Bentham science Rehabilitation 5: 14-21.

52. Onders RP, Elmo MJ, Khansarinia S, Bowman B, Dunkin B, et al. (2009) Complete worldwide operative experience in laparoscopic diaphragm pacing: results and differences in spinal cord injured patients and amyotrophic lateral sclerosis patients. Surg Endosc 23:1433-1440.

53. Memberg WD, Peckham PH, Keith MW (1994) A surgically-implanted intramuscular electrode for an implantable neuromuscular stimulation system. IEEE Trans Rehab Eng 2: 80-91.

54. Walter JS, Wurster RD, Zhu Q, Laghi F (2011) Respiratory Muscle Pacing with Chronically Implanted Intramuscular Permaloc® Electrodes: A Feasibility Study. J Rehab Res Dev 48: 103-114.

55. Walter JS, Thomas D, Sayers S, Perez-Tamayo A, Crish T, et al. (2014) Respiratory Responses to Stimulation of Abdominal and Upper-Thorax Intercostal Muscles Using Multiple Permaloc® Electrodes. J Rehab Res Dev in press.