Invasive Therapies in Multiple Sclerosis

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ABSTRACT

Multiple sclerosis is a progressive disease despite so many recent therapy agents. Many symptoms can be seen that can affect the quality of daily life, such as spasticity, urinary incontinence, sensory disturbances, and tremor. These complaints may be refractory to the medical treatments, and the invasive treatment methods may be the only option to improve the quality of life of the patient. Intrathecal baclofen pump therapy can effectively reduce the spasticity in a patient with an inadequate response to oral baclofen. On the other hand, deep brain stimulation significantly reduces tremor and can provide the patient to eat by his/her self. Sacral neuromodulation may be beneficial in a patient with a history of urge incontinence which doesn't respond to oral agents. Adequate pain control can be achieved with spinal cord stimulators when a patient is

unresponsive to the neuropathic pain treatment. Common features of all these invasive therapies are that they are used in patients who do not respond to medical treatments, they have a small number of randomized controlled clinical trial, and almost all of them are incompatible with MRI devices. According to the latest researches, more randomized controlled clinical trials and MRI compatible devices have been produced in recent years. We wanted to discuss these treatment methods even they have not yet been used routinely. We think they would be beneficial in clinical practice after their deficiencies have been overcome.

Keywords: Multiple sclerosis, deep brain stimulation, sacral neuromodulation, intrathecal baclofen, spinal cord stimulation

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INTRODUCTION

Progressive disability may occur despite a large number of immunomodulatory drugs and monoclonal antibodies used in the treatment of multiple sclerosis (MS). Concomitant pathologies such as spasticity, urinary incontinence and tremor may significantly impair the patient's daily activities. Invasive treatment options should be considered if these accompanying complaints do not respond to medical treatments. Although invasive treatment modalities have been mostly used for movement disorders and stroke-related pain in neurological practice, they have also been used in patients with MS. For example, intrathecal baclofen pump (ITB) may be a good option for patients with spasticity, and spinal cord stimulators (SCS) are useful in patients with urinary incontinence. There are also other invasive therapies, such as functional electrical stimulation, sacral neuromodulation (SNM) and deep brain stimulation (DBS). Although many of these invasive therapies are not yet in routine use, it is becoming increasingly widespread in recent years. In this article, we tried to summarize the invasive methods used in the symptomatic treatment of patients with MS.

Intrathecal Baclofen Pump Therapy

Spasticity can occur in many diseases such as stroke, traumatic spinal cord injury, cerebral palsy and MS. It is one of the most critical

conditions which affects patient's ambulation and daily life activities. The clinician can use baclofen and tizanidine as oral anti-spasticity agents. Despite maximum oral doses of this therapies, MS-related spasticity can be resistant and require invasive treatments (1). ITB pump was first developed in 1984 by Kroin and Penn, but its use in patients with MS is still limited. The ITB pump consists of two parts: a reservoir and a catheter. The reservoir is implanted into the lower abdominal skin. Liquid baclofen is transferred via catheter ending mostly in the thoracic 10–11 level (2). As we know that oral baclofen has some side effects such as sedation, confusion, hypotension, and nausea. The reason for the occurrence of these side effects depends on the rapid increase in the blood concentration of the drug. Unlike oral baclofen, these side effects are less noticeable with the ITB pump therapy because the intrathecal dose of baclofen is approximately 1% of the oral equivalent. The programmable pump allows for appropriate and continuous administration of baclofen into the intrathecal space. As a result of this, a constant level of drug is obtained, and sudden changes in drug concentration are avoided (3). Patient selection criteria for ITB pump therapy in MS patients are the same as those for the general population. The primary indications are the insufficient response and tolerability problems to oral baclofen. Before the decision of the ITB

pump therapy, a test dose must be applied. Before the test dose, the Modified Ashworth Spasticity Scale (MASS) is measured. Liquid baclofen is administered via lumbar puncture, at least one point improvement of MASS is expected after the administration, and the clinician should be alert for the weakness/flaccid tonus due to intrathecal baclofen. If flaccid tonus occurs, the mobilization of the patient will deteriorate, and therefore the ITB pump therapy will be inappropriate (4). The ITB pump therapy has some advantages. The clinician can change dosage with the aid of an externally adjustable device. Less systemic side effects are seen with the intrathecal administration and provide a consistent treatment chance by eliminating oral medication need. With this treatment procedure, it is possible to reduce the amount of oral drug and prevent the drug interactions. On the other side, ITB pump treatment has some disadvantages. The best known are surgical procedures, catheter dysfunction, and catheter infection. The other potential problems are life-threatening withdrawal and requirement of recurrent surgeries due to the limited battery life (5). ITB pump therapy is mostly applied to immobilized MS patients. The primary goals of this therapy for immobilized patients are to improve posture disturbances, providing perineal hygiene, relieving pain and sleep disorders caused by spasticity. It also allows improving cognitive decline by reducing the use of sedative agents (oral baclofen) (6). But on the other hand, McCormick and his colleagues reported no significant difference in pain, sleep, fatigue, and quality of life between intrathecal and oral baclofen groups. They only found a significant difference in spasm frequency and severity and offered to consider the potential risks of ITB pump use instead of oral baclofen (7). Despite the widespread use of this treatment in immobilized patients, ambulatory patients also need to be used. In ambulatory patients, ITB pump therapy meliorates sleep disturbances, depressive symptoms, and pain related to spasticity. For ITB pump therapy, it is not appropriate to wait until the spasticity has reached the level where the patient will be sentenced to a wheelchair. They are more involved in daily life, and early treatment will be better to keep the patient's ambulation (8). The ITB pump therapy dosing regime changes between diagnoses and tends to differ by ambulatory status. According to Clearfield, MS patients require lower doses according to stroke, cerebral palsy and traumatic spinal cord injury patients (9). According to another research, the baclofen dosage has stabilized within two years in multiple sclerosis patients at 323 µg/day; while spinal cord injured patients have reached a stable dosage within five years at 504 µg/day. Investigators also found a complication rate of 1% per month and most complications are due to catheter-related problems and infections (10).

Despite all these complications, ITB pump therapy is safe in pregnancy, and adverse effects are rare and temporary due to recurrent magnetic resonance imaging (MRI). ITB is also useful in long-term and improves both the patient's and caretaker's quality of life. In the end, ITB pump therapy should be administered in selected cases (11).

Spinal Cord Stimulation

For almost 40 years, SCS had been used in different conditions such as spinal cord injury, cerebral palsy and spasmodic torticollis. In 1973, Cook and Weinstein firstly observed in an MS patient that SCS can be useful for treating neuropathic pain. Nowadays, SCS is usually used to treat medical treatment-resistant neuropathic pain and bladder dysfunction in MS patients. The exact mechanism of SCS is not known. It is thought that SCS leads to functional changes at the cellular level, reduces neurotransmitter release, and blocks pain signals at dorsal columns (gate control theory) (12). SCS, which is an invasive treatment method, is applied surgically to the patient. This device consists of four parts. These are electrode leads, an extension cable, an implanted pulse

generator (IPG) and a programmer. Mostly percutaneous leads are used. Test stimulation should be done before the permanent application to see if the patient will benefit from the treatment. If the test stimulation is successful, percutaneous leads are introduced in the central epidural space to stimulate dorsal columns. These electrode leads are connected to the IPG via an extension cable, and the IPG is mostly implanted in the lower back (13). The literature on SCS in MS patients is limited. Most of them have been done with a small number of patients, and the studies are quite old. In 1980, a review of 19 patients by Illis et al. was an outstanding start. Motor and sensory findings improved in 27%, and 75% of the patients had a positive effect on bladder function. In another study done by Read et al. in the same year, beneficial effects on bladder functions and lower extremity spasticity were determined (14). Similarly, Peters et al. found that SCS has a significant impact on urinary symptoms in a cohort of patients with MS, stroke, and Parkinson disease (15). Cook et al. reported improved bladder, motor, and sensory functions. Interestingly they also observed enhanced cerebellar functions by treating upper extremity ataxia (16). SCS can also be used to treat thalamic origin pain. In 2009, Lopez et al. reported eight individuals, including 2 MS patients. Patients were treated with SCS in the cervical or dorsal cord, and most patients were pain-free in long-term follow (17). In addition to studies in the literature, many case reports also suggest that SCS may be useful. Burkey reported a 52 years old woman presented with hand pain caused by cervical spinal cord demyelination. They applied an SCS in the cervical cord, and within one year, the pain showed a significant decrease (18). Provenzano also presented a 68-year old man, having bilateral lower extremity pain. After two years of follow-up, he had a 77% reduction in the pain and a 99% decrease in opioid consumption were observed (19). As in DBS, SCS also has some difficulties such as IPG infection, lead breaks, and lead displacement (20). Another big problem related to SCS is MRI. The sound waves emitted from the MRI device can disrupt the functions of the IPG, can cause to the system malfunction, and can even damage the patient with overheating. For this reason, SCSs compatible with MRI devices have been developed in recent years (21). Consequently, SCS appears to be useful in bladder functions and neuropathic pain. The effects on motor, cerebellar and sensory functions are unclear. More researches are needed to investigate the effects of SCS.

Deep Brain Stimulation

DBS is almost gold standard therapy for the medical treatment-resistant Parkinson disease, essential tremor (ET), and generalized dystonia (22). It is a surgical procedure targeting the specific nuclei such as ventral intermediate nucleus (VIM), ventralis lateralis (VL) nucleus, ventralis oralis posterior (VOP) nucleus, and zona incerta (ZI) (23). Before applying DBS, the MRI should be done to determine the coordinates of the target nucleus. Stereotactic surgery is performed with these coordinates, and stimulating electrodes are placed in the localization of the target nuclei. During the operation, the patient is awake, and the patient is asked to evaluate the response of their symptoms to stimulation. If correct localization is achieved and improvement of the patient's symptoms is detected, stimulating electrodes are attached to the IPG placed under the clavicle. After the operation, the magnitude and frequency of the DBS signal can easily be changed via the external control unit according to the patient's symptoms (24). The effect of DBS is reversible, doesn't lead to tissue destruction like thalamotomy or pallidotomy, and seems effective. The exact mechanism is still not known, but the blockage of the action potential, stimulation of neurotransmitter release and improving axonal firing or combination of these possibilities are thought to be the potential mechanisms.

Many symptoms are affecting the patients with MS such as motor weakness, ataxia, tremor, bowel and bladder dysfunction and cognitive

impairment. Among them, tremor is one of the most disabling symptoms in patients with MS. Especially it can impair handwriting, fine motor skills, feeding, and working life (25). The prevalence of tremor varies between% 25 to% 55, and in this patient group, clinically disabling tremor is seen approximately% 5 to% 25 (26, 27). Besides being one of the most disabling symptoms, it is one of the most resistant symptoms to medical treatment. The main indication for DBS surgery is treatment resistant upper extremity tremor. It is important for the clinician to distinguish between tremor and ataxia before applying DBS. The general approach for MS tremor is unilateral or bilateral thalamic VIM stimulation. Tremor ratios decrease with VIM stimulation, but this may not always be a functional improvement (28). Also, VIM stimulation is not effective on proximal tremor, and over time the positive effect on tremor may be lost. For this reason, researchers investigated the effects of different localizations on tremor. Whittle reported four patients with bilateral VL stimulation. He detected an improvement in tremor and functional status and no adverse events were observed (29). After then Nandi reported ten patients with bilateral VOP+ZI stimulation. The tremor was suppressed by a combination of VOP and ZI stimulation (64 and 36% improvement for postural and intention tremor, respectively) (30). Hamel also introduced two patients with bilateral VL+Subthalamic nucleus (STN) stimulation, and he reported that suppression of intention tremor was more effective with STN stimulation more than VL stimulation (31). Plaha et al. detected a significant improvement in all tremor types with bilateral ZI stimulation in four patients (32). After five years follow up, Thevathasan et al. reported sustained improvement in% 50 of limbs affected by the tremor in 11 patients (33). In 2018, Artusi et al. reported a paper including 177 patients with MS who underwent DBS surgery for tremor. VIM approach was applied to 146 of 177 patients. (93 unilateral, 26 bilateral, 25 VIM plus STN or VO). Symptom improvement was reported in 126 of 146 patients, but 20 patients had a transient response. 25 patients had a ZI DBS surgery (4 bilateral, 21 bilateral ZI+VOP) and six patients underwent on a VL DBS surgery (4 bilateral, 2 VL+STN). They also reported complications related to the procedure. These are intracerebral hemorrhage, infections, stimulation induced paresthesia, dysarthria, gait ataxia, transient hemiparesis, seizures and the worsening of MS symptoms. As MS symptoms may worsen, some authors suggest that high-dose IVMP may be given before surgery. But we still don't know how accurate this recommendation is (34).

Another use of DBS therapy is facial pain treatment. Facial pain due to trigeminal neuralgia (TN) occurs almost% 2–5 of patients with MS (35). Carbamazepine, pregabalin, and amitriptyline can be used as pharmacological treatment, and microvascular decompression is the surgical option for treating medically intractable TN (36–38). As in TN, the main target nuclei in pain treatment are Ventralis posterolateralis (VPL)/Ventralis posteromedialis (VPM). (39) Beside VPL/VPM, the other possible localizations are the periaqueductal grey area (39), posterior hypothalamus (40), and anterior cingulate cortex (41). There is only one study, reported by Cordella, including five patients with MS-related TN. All these patients were medically intractable, and percutaneous balloon compression was unsuccessful. One patient was pain-free, and the other four patients had pain, but the pain could be controlled with medications, after applying posterior hypothalamic DBS. One of the important problems related to DBS is the MRI requirement. In the last decades, DBS devices were incompatible with MRI, but now we have new DBS hardware compatible with full body MRI (42).

In summary, DBS can be a good option for treating medical intractable tremor and body pain in patients with MS. In contrast to VIM approach, ZI, VOP, and VL may be the new targets for DBS. MR compatible devices

will be useful to reach more patients, and lastly, the clinician should be careful in patient selection.

Sacral Neuromodulation

MS is generally associated with low urinary tract (LUT) dysfunction. It is common in the progressive phase, but may also occur in initial stages (43). Patients may experience problems related to storage or voiding. Overactive bladder is a storage problem, and the patient may present with urgency, frequency, and urinary incontinence. As tremor or ataxia, LUT dysfunction is a huge problem for the quality of life. The social and work life of patients who have to use underpads due to urinary incontinence are significantly affected (44). Therefore, the clinician should pay attention. There are some treatment options for LUT dysfunction. Antimuscarinics are the first choice such as darifenacin, oxybutynin, solifenacin, tolterodine and trospium chloride. Mirabegron, alpha-1 blockers, desmopressin, phosphodiesterase type 5 inhibitors and cannabinoids are the other agents that may be useful in overactive bladder symptoms. Botulinum toxin-A, vanilloids, and oxybutynin are the intravesical treatment alternatives (45). More invasive treatment options can be used in cases resistant to all these treatments. SNM is a surgical procedure, implanting the stimulation electrode on the pelvic nerves (mostly S3) to improve overactive bladder symptoms in treatment-refractory cases (46). Kessler et al. reported >% 50 improvement in pad use, leakages, and the number of catheterizations (47). Minardi et al. found beneficial effects of SNM in patients with MS such as a decrease in residual volume with an increase in voided volume and number of voiding per day (48). Wallace also reported research with SNM in a mixed neurological patient group. In his trial, most of the patients were MS, and he detected a significant reduction in pad use, incontinence episodes and day and night-time frequency (49). Marinkovic et al. applied SNM to 12 female MS patients who have refractory LUT dysfunction. The mean follow-up was four years. After the research, they reported a significant reduction in postvoiding bladder volume and number of self-catheterization per day (50). Despite these beneficial effects of SNM, being MR incompatible is still a big problem, especially for patients who require routine MR imaging. But some authors have reported that the 1.5 Tesla MR device can be used without safety concerns (51). As a result, SNM may be helpful for treating MS-related overactive bladder symptoms, but more randomized controlled trials are required.

CONCLUSION

MS is characterized by many symptoms that can affect daily life such as motor weakness, sensorial disturbances, spasticity, tremor, pain and overactive bladder symptoms. We have lots of medical options for all these symptoms, but due to the progressive course of the disease, sometimes we have to apply invasive treatments. ITB pump therapy seems helpful for spasticity and DBS may be useful for tremor and TN. SCS appears to be effective in bladder functions and neuropathic pain, but the effects on motor, cerebellar and sensory functions are unclear. Also, SNM can be beneficial for treating refractory overactive bladder symptoms. Despite all these positive effects, there is a need for randomized controlled clinical trials involving more patients for invasive therapies to be used routinely.

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