Neuromodulation Using Intrathecal Baclofen Therapy for Spasticity and Dystonia

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Abstract

Intrathecal baclofen (ITB) therapy is a treatment for intractable spasticity due to a variety of causes. Continuous intrathecal administration of baclofen, an agonist of the inhibitory neurotransmitter \( \gamma \)-aminobutyric acid, inhibits excitation of motor neurons at the spinal level and thus suppresses spasticity. This therapy was introduced clinically in the Europe and the United States in the 1990s, and was finally approved by the Japanese Ministry of Health, Labour and Welfare in Japan in 2005. Clinical use has been permitted since 2006, and reports of therapeutic efficacy are now appearing in Japan. ITB therapy is a non-destructive treatment that enables administration of baclofen from an implantable pump under the control of a programmer, and represents an outstanding treatment method offering both reversibility and adjustability. Indications for ITB therapy have been expanding in recent years to include not only spasticity, but also various causes dystonia. And ITB therapy can greatly improve activities of daily living and quality of life, and this treatment is attracting attention as a neuromodulatory therapy that also affects metabolic and respiratory functions and even state of consciousness. We here report the surgical methods and therapeutic outcomes for 22 patients who underwent ITB therapy for spastic and dystonic patients in our hospital, together with an investigation of the effects on metabolic and respiratory functions.

Key words: neuromodulation, intrathecal baclofen, spasticity, dystonia

Introduction

Spasticity is a form of upper motor neuron syndrome caused by central nervous system dysfunction due to stroke, traumatic head injury, spinal injury, cerebral palsy, or other causes, and manifests as motor disorder characterized by a velocity dependent increase in tonic stretch reflex (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex, as one component of the upper motor neuron syndrome. Upper motor neuron syndrome causes positive symptoms including spasticity, spastic dystonia, and synkinesia, as well as negative symptoms of motor paralysis and reduced dexterity, giving rise to a range of motor disturbances. Motor paralysis and similar symptoms are mainly treated with rehabilitation, but positive symptoms such as excessive spasticity and spastic dystonia not only hinder rehabilitation, but also reduce activities of daily living and quality of life, making management an extremely important issue.

Baclofen acts as an agonist to the bicuculline-insensitive type of \( \gamma \)-aminobutyric acid (GABA) receptor known as GABA-B. There is a high density of GABA-B receptors in the dorsal horn of the spinal cord. Activation of presynaptic GABA-B receptors causes an inhibition of calcium-mediated inward current, thus inhibiting the release of excitatory neurotransmitters such as aspartate and glutamate in the polysynaptic pathways of the dorsal horn. This alters and reduces the excitability of monosynaptic and polysynaptic reflexes. Baclofen is thought also
to exert a postsynaptic action, which also reduces reflex excitability. Baclofen has been used as an oral medication to alleviate spasticity for over 30 years, but as it shows minimal penetration of the blood-brain barrier, the high doses required meant that clinically satisfactory improvements in spasticity could not be achieved. Intrathecal administration of baclofen (ITB) enables direct action on the spinal cord, and has been demonstrated to improve spasticity at far lower doses compared with oral administration. Single intrathecal administration for human spinal spasticity was first reported by Penn in 1984, and continuous administration via an implantable pump was performed for patients with spinal spasticity such as that caused by multiple sclerosis or traumatic spinal injury. Efficacy was subsequently reported from clinical trials carried out in Europe and the United States. Food and Drug Administration granted approval in 1992.

Since then the indications for ITB therapy have been expanding to not only spasticity from spinal origin, but also spasticity associated with cerebral palsy and traumatic brain injury. Significant effects of ITB therapy on severe spasticity have subsequently been confirmed, as has maintenance of this effect during long-term administration. In 2005, this procedure was finally approved in Japan, clinical use has been permitted since 2006, and reports of efficacy are now appearing in Japan. ITB therapy is a non-destructive treatment that is administered from an implantable pump under the control of a programmer, offering an outstanding treatment method that provides both variability and adjustability. This approach is now attracting attention as a neuromodulatory therapy. In recent years, indications for ITB therapy have been expanding in other countries to include not only spasticity, but also dystonia and other type of spastic hypertonia. In Japan, the total number of clinical cases receiving ITB therapy for spasticity has now reached around 600, but few reports have described clinical use for dystonia. We report the surgical methods and therapeutic outcomes of 22 spastic and dystonic patients who underwent ITB therapy in our hospital, together with an investigation of the effects on metabolic and respiratory functions.

## Patients and Methods

Baclofen screening tests were performed on 30 patients with hemiplegia, paraplegia, or tetraplegia who exhibited diffuse spasticity or dystonia due to central nervous system dysfunction. This study included 22 patients for whom symptoms improved. The underlying pathology was intractable spasticity in 19 patients, 6 caused by cerebrovascular accident.

### Table 1 Clinical characteristics of 22 patients with spasticity and dystonia

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<tr>
<th>Case No.</th>
<th>Age (year)</th>
<th>Sex</th>
<th>Underlying illness</th>
<th>Time since onset (month)</th>
<th>Symptom</th>
<th>Catheter placement</th>
<th>Metabolic examination</th>
<th>Respiratory examination</th>
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2 by traumatic brain injury, 3 by adult spastic cerebral palsy, 4 by spinal cord injury, 1 by spastic paraplegia, 1 by medullary degenerative disease, 1 by syringomyelia, and 1 by spinal multiple sclerosis; and secondary generalized dystonia in 3 patients, 1 caused by cerebrovascular accident and 2 by traumatic brain injury (Table 1). The type of dystonia in our patients manifested as extensor posturing of body trunk and all limbs with intermittent tachypnea, tachycardia, hyperthermia, and agitation.

If the main symptoms were located in the spastic lower limbs, the intrathecal catheter was placed at the lower thoracic spine level (T10–T12) via a paramedian puncture at the L2-3 or L3-4 level (posterior lumbar spine approach). In cases of spastic tetraplegia and generalized dystonia, a catheter cannot be placed at the cervical spine level (C1–T2) via the translumbar approach, because Japanese intrathecal catheters measure only 38.1 cm in length. Catheters were therefore placed at the cervical spine level (C1–T2) via the T7-8 level by direct insertion of catheter to the subarachnoid space under unilater hemilaminectomy under microscopic guidance (posterior thoracic spine approach). The ITB pump was placed subcutaneously or beneath the fascia of the rectus abdominus in the lower abdomen. Surgical response was determined by measuring Ashworth score (Table 2) of affected limbs before and 6 months after the procedure.

Respiratory gas analyzer was used to measure resting metabolic rate before and 1 month after the procedure in the most recent 10 patients who underwent ITB therapy (Cases 13–22). The ratio of actual measured values was evaluated against the standardized resting metabolic rate for the Japanese individuals of the same age, height, and weight as the patients. Effects on respiratory function were also measured and evaluated in the same 10 patients using polysomnography before and 1 month after the procedure.

Results

Mean daily dose of ITB therapy was 171.6 µg/day (range 60–344.5 µg/day) for the 22 patients, and the mean duration of follow up was 25 months (range 6–53.8 months).

Lower limb spasticity was evaluated using the Ashworth score before and 6 months after the procedure. Mean Ashworth score for the affected lower limbs when the intrathecal catheter was placed at the lower thoracic spine level (n = 28) improved from 3.07 to 1.69, representing a highly significant difference (p < 0.0001, paired t-test), and mean Ashworth score for the affected lower limbs when the intrathecal catheter was placed at the cervical spine level in tetraplegia and dystonic patients (n = 18) improved significantly from 3.68 to 2.61 (p < 0.0001, paired t-test). Lower limb spasticity exhibited highly significant improvement regardless of catheter position (Fig. 1). On the other hand, mean Ashworth score for the affected upper limbs when the intrathecal catheter was placed at the lower thoracic spine level (n = 11) improved significantly from 2.87 to 2.30 (p = 0.004, paired t-test), and mean Ashworth scale for affected upper limbs when the intrathecal catheter was placed at the cervical spine level (n = 18) exhibited highly significant improvement from 2.72 to 1.88 (p < 0.0001, paired t-test). Upper limb spasticity exhibited more significant improvement when the catheter was placed at the cervical spine level (Fig. 2). In hemiplegic patients, spasticity on the affected side improved with no loss of muscle strength in the unaffected limb, and in ambulatory patients with spastic paraplegia, control was achieved at a low baclofen dose of approximately 60 µg/day.

![Fig. 1 Mean Ashworth score (AS) for the affected lower limbs before and 6 months after the procedure when the intrathecal catheter was placed at the lower thoracic spine level (left) or at the cervical spine level (right). *p < 0.0001, paired t-test.](image)
Fig. 2 Mean Ashworth score (AS) for the affected upper limbs before and 6 months after the procedure when the intrathecal catheter was placed at the lower thoracic spine level (left) or at the cervical spine level (right). *p = 0.004, **p < 0.0001, paired t-test.

Fig. 3 Standardized resting metabolic rate (Std. RMR) and mean Ashworth score (AS) before and 1 month after the procedure in 10 patients who underwent metabolic measurement. CP: cerebral palsy, CVA: cerebrovascular accident, DYS: dystonia, MDD: medullary degenerative disease, SCI: spinal cord injury, SM: syringomyelia, TBI: traumatic brain injury.

All 10 patients who underwent metabolic measurement exhibited resting hypermetabolism before the procedure, which declined after the procedure. This reduction was particularly marked in patients with dystonia and cerebral palsy, for whom metabolic rate had been over 1.5 times the normal value before surgery. Mean Ashworth scale of affected limbs also decreased, showing a similar improvement in spasticity to the reduction in resting metabolism (Fig. 3).

The apnea-hypopnea index (AHI) per hour of sleep was evaluated before and 1 month after the procedure in the same 10 patients who underwent metabolic measurement. Before this procedure, AHI was normal (AHI 0–4) in 3 patients, mild (AHI 5–14) in 4, moderate (AHI 15–30) in 2, and severe (AHI >31) in 1. The 3 patients with severe or moderate AHI scores improved markedly, whereas 4 of the 7 patients with normal or mild scores showed improvement, and no change was seen in the 3 remaining patients. Sleep apnea thus improved or remained unchanged in all cases, and did not worsen in any patient (Fig. 4).

Complications included catheter displacement in 2 patients, catheter fracture in 1 patient, and pump infection in 1 patient.

Discussion

Albright suggested that in ITB therapy, intrathecal catheter placement should be at the lower thoracic spine level (T10–T12) if spasticity or dystonia mainly affects the lower limbs, at the upper thoracic spine level (C5–T2) if the upper limbs are affected, and at the cervical spine level (C1–C4) if all four limbs and the trunk are affected, as in generalized dystonia. When ITB therapy was introduced in Japan, it was used to treat lower limb spasticity, and the basic placement position of the intrathecal catheter was at the lower thoracic spine level (T10–T12). The effectiveness of this method was ex-

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Extremely high, as reported in Europe and the United States. Indications were later expanded to encompass spasticity not only of the lower limbs, but also of the upper limbs and trunk, but only one type of intrathecal catheter (length 38.1 cm) has been introduced for ITB therapy in Japan. This system cannot be placed at the cervical spine level or upper thoracic spine level using the posterior lumbar spine approach. For this reason, efficacy for arm and trunk spasticity is unreliable. We therefore developed the posterior thoracic spine approach. This method enables catheter placement at the cervical spine level, ensuring effectiveness for secondary generalized dystonia and upper limbs and trunk spasticity, and we demonstrated that Ashworth score improved with high significance after the procedure compared with lower thoracic spine level catheter placement. Catheter placement at the cervical spine level was also considered to have the potential for reduced effectiveness on the lower limbs, but we confirmed that sufficient response was also obtained in the lower limbs, again exhibiting significance. Should the longer intrathecal catheters used in Europe and the United States be approved for use in Japan in the future, intrathecal catheters could then be placed at the cervical spine level using the standard posterior lumbar spine approach, reducing the invasiveness of ITB and creating simple indications for patients with tetraplegic spasticity or generalized dystonia.

In hemiplegic patients, spasticity on the affected side improved with no loss of muscle strength occurring in the unaffected limb. Other studies demonstrated similar findings. It is still unclear why the uninvolved limbs are not affected by ITB, at least clinically. Perhaps ITB has a selective effect on certain spinal cord receptors that also receive supraspinal input modified by the cerebral disease. Or maybe the small amount of baclofen in the intrathecal space may not be enough to produce clinically detectable weakness. This is one observation that still needs further investigation to have a better understanding of the mechanism of action of ITB at the cellular level.

In most cases, the effectiveness of ITB therapy is determined in terms of the change in Ashworth score as an evaluation of spasticity, and few reports have applied other evaluation methods. We realized that patients with spasticity or dystonia exhibit hypermetabolism due to spastic hypertonia, and investigated to what extent improvement of spastic hypertonia as a result of treatment affects metabolic function by measuring resting metabolism using a respiratory gas analyzer. All 10 patients for whom resting metabolism was measured exhibited resting hypermetabolism before the procedure, which declined in all patients after the procedure. This reduction was particularly marked in the 3 patients with dystonia and the 2 patients with spastic cerebral palsy, for whom resting metabolic rate measured before surgery was over 1.5 times the standardized value for their sex, age, height, and weight. This finding shows that spastic hypertonia contributes greatly to hypermetabolism, a result that underlines the necessity of treatment, since untreated continuation of this hypermetabolic condition would influence future cardiopulmonary function, and potentially affect the survival of the patient. Metabolic function also tended to correlate with improvements in Ashworth score, and we considered that metabolic function should be utilized in adjusting ITB treatment after the procedure.

On the other hand, spasticity has been reported as primarily a physiological response to prevent the fatty metamorphosis of muscles that have fallen into motor paralysis, and as such represents a necessary process. Therefore, ITB therapy should not reduce muscular tonus more than required. Moreover, weight gain has been observed clinically in patients undergoing ITB therapy, although published reports of this side effect are rare, but weight gain constitutes a major cause of hypometabolism. Our results also suggest that the reduction of spasticity and metabolic rate may be involved, and that adjusting the dosage of baclofen to bring resting metabolism into line with the standardized value for the age, weight, and height of the patient may enable better control of spasticity and dystonia. Future studies involving more patients are required to investigate the use of resting metabolism with more reliable response evaluations.

Few previous reports have examined the effects of ITB therapy in patients with respiratory dysfunction. ITB therapy was performed in patients with mixed spastic-athetoid tetraplegic cerebral palsy with dystonia who required nocturnal continuous positive airway pressure (CPAP) therapy for obstructive apnea-hypopnea. Not only did this alleviate spasticity and dystonia, but subsequent sleep respiratory tests also showed that obstructive apnea-hypopnea had resolved and CPAP therapy was no longer required. This was attributed to two effects of ITB therapy: improved vital capacity due to the alleviation of respiratory muscle spasticity; and reduced sleep apnea due to improved respiratory muscle synchronization thanks to the alleviation of dystonia. Investigation of the effects of ITB therapy on sleep and respiratory function in 20 patients with severe spasticity found that ITB therapy enabled continuous sleep to be achieved, improving sleep ef-
ficiency, with no change in sleep respiratory events or daytime respiratory function tests, meaning that respiratory function was no longer impaired either during the day or at night. ITB therapy delivers an extremely small dose directly to the site of action in the spine without reference to the blood-brain barrier system compared with oral medication. This means that few systemic side effects are produced.

Some reports have indicated that sleep apnea may occur as a result of traumatic brain injury. Obstructive sleep apnea was evident in 23% of 87 patients at ≥3 months after injury, and in 30% of 54 patients between 3 months and 2 years after injury. Our patients, who showed severe spasticity for which ITB was indicated, also included patients with severe or mild sleep apnea, and ITB therapy should perhaps be considered for patients with respiratory disturbance that is successfully managed with CPAP therapy or similar and in whom other treatments for spasticity are ineffective. Recently, a significant increase of respiratory events was reported to be associated with the bolus mode of ITB therapy. In contrast, continuous infusion mode did not induce a significant modification of sleep-disordered breathing. It is probably better to use a continuous mode of infusion if patients have preexisting sleep-disordered breathing. We also confirmed that the continuous infusion mode of ITB therapy improved the AHI in this study, indicating that ITB therapy does not necessarily have negative effects on respiratory function, but rather that it offers a safe method of treatment that can be expected to result in functional improvement.

The most common complications of ITB surgery were catheter-related problems (31%), seromas (24%), and cerebrospinal fluid leaks (15%). Complications occurred in 31% of patients as follows: 11% had cerebrospinal fluid leakage, 7% had catheter-related problems, 7.5% suffered infections, and 5.5% of patients had more than one complication. Our complication rate was 18.2% (catheter displacement in 2 patients, catheter fracture in 1 patient, and pump infection in 1 patient) indicating better results than these previous studies.

Intractable spasticity and dystonia are complicated by severe hypermetabolism and sleep apnea, which necessarily has negative effects on activities of daily living and quality of life, and we have confirmed that these measures are improved when spasticity and dystonia are alleviated by ITB therapy. ITB therapy may be further expected to serve as a neuromodulation treatment in functional neurosurgery.

References
15) Lance J: Symposium synopsis, in Feldman RG,


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