Spasticity Patients: Special Considerations

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ABSTRACT

Spasticity is a frequent symptom of central nervous system disorders, and in many patients has a significant subjective and objective impact. Intrathecal baclofen (ITB) therapy is increasingly utilized to treat severe spasticity refractory to oral antispasticity medications, based on a growing body of evidence demonstrating its efficacy in various conditions. Because ITB involves significant risks, careful patient selection, thorough multidisciplinary patient evaluation and education, treatment planning, standardized surgical techniques, and aggressive management are required to maximize treatment benefits. Further research is needed to explore the long-term effects of ITB on function and subjective health status.
Key words: spasticity, intrathecal injection, central nervous system.

Spasticity has been defined as a velocity-dependent increase in resistance to passive muscle stretching due to the exaggeration of tonic stretch reflexes.[1] Spasticity is encountered in a variety of conditions affecting the central nervous system (CNS). It is estimated that at least 500,000 persons in the United States present with some degree of spasticity. Decreased descending inhibitory signals secondary to damage to the CNS, with resultant hyperactivity of GABAergic intramedullary oligo- or polysynaptic pathways, is thought to be the main mechanism causing spasticity.[2] Two subtypes of spasticity, have been defined: spasticity of cerebral origin and spasticity of spinal origin. Although the pathophysiology of spasticity is incompletely understood, many symptomatic therapies are available to the clinician. Over the past 13 years, intrathecal (IT) therapy has emerged as an effective treatment for severe spasticity refractory to other treatment modalities.

Consequences of Spasticity

Spasticity is part of the upper motor neuron (UMN) syndrome, which includes positive (increased muscle tone, exaggerated tendon reflexes, spread of stretch reflex, clonus, synergy patterns, Babinski sign) and negative (loss of dexterity, weakness) signs and symptoms. Patient- and caregiver-reported consequences of spasticity include muscle stiffness (tightness) and/or spasms, pain or discomfort, loss of function in upper/lower extremity, difficulty maintaining standing and/or sitting postures, and decreased ease of care or self-care (eg, difficulty performing intermittent catheterization due to hip adductor spasticity). Objective manifestations of spasticity can be divided into dynamic phenomena (abnormal voluntary movements, synergy patterns, and spontaneous or easily triggered involuntary movements such as clonus or spasms) related to reflex hyperexcitability, and static phenomena (decreased range of motion) caused by changes in the rheologic properties of musculoskeletal structures. In many patients, spasticity causes or contributes to limitations in activities and social participation, and decreased quality of life. Severe spasticity may lead to fixed contractures, confining the patient to bed and increasing the risk of medical complications such as decubiti or infections. However, spasticity can also be beneficial and, in particular, may help preserve the ability to stand and walk in patients with severe

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lower extremity weakness. Spontaneous fluctuations of spasticity over time complicate its assessment and management. Sudden increases in spasticity should trigger a search for a noxious stimulus (eg, pain, decubiti, urinary tract infection, ingrown toenail, changes in ambient or body temperature) or exacerbation/progression of the causal CNS disorder.

Assessment of Spasticity

The evaluation of spasticity and its consequences should be multidimensional. Patient-or caregiver-reported complaints and clinical examination are the most widely used assessment techniques in routine practice and in clinical trials. To standardize and quantify these parameters, widely accepted and easy-to-use validated outcomes measurement tools include the Ashworth Scale[3] (and Modified Ashworth Scale[4]), the Spasm Frequency Scale,[5] and the 10-cm pain visual analog scale. However, the psychometric properties of these scales are not optimal, and they do not capture the whole spectrum of consequences of spasticity. Quantitative tests, such as the pendulum test,[6] the vibration inhibitory index (VII),[7] the H-reflex, and H_{max}/M_{max} ratio, are too cumbersome to be used in routine practice and are not always correlated with other clinical measures.

When considering an aggressive treatment modality such as intrathecal therapy, it is essential to evaluate the effects of spasticity on care or self-care, function, participation, and quality of life. In routine practice, this can be done by careful and thorough interview, combined with physical and occupational therapy assessments. Quantitative measures of disability and quality of life, both useful for clinical and research use, can be classified into generic (eg, Functional Independence Measure, timed 25-foot walk or 6-minute walk for gait performance, nine-hole peg test for upper extremity function, SF-36, or Sickness Impact Profile for quality of life) and disease-specific instruments. Generic measures allow comparisons across pathologic conditions, whereas disease-specific measures are often more clinically relevant and sensitive to change, and both types can be combined into comprehensive batteries.

Intrathecal Therapy for Spasticity

Situating IT Therapy in the Spectrum of Treatments for Spasticity

IT therapy for spasticity, although currently underutilized, is indicated in a small fraction of patients with CNS disorders. As part of an integrated model of care, it is often considered after other treatment modalities have failed, but does not necessarily preclude the continued use of these modalities.

Rehabilitative interventions. Rehabilitation (physical therapy and occupational therapy) is indicated at all stages of spasticity. It is often used in combination with other treatments, although stretching alone can be sufficient to achieve a good control of mild spasticity. Education and the development of home exercise programs are essential. As appropriate, gait/balance or upper extremity functional training, adaptation of orthoses and assistive devices, or even vocational rehabilitation can be used to help the patient achieve a better level of function in his/her environment. In intractable spasticity, the main focus is preserving the range of motion through aggressive stretching and range-of-motion (ROM) exercises, splinting, or serial casting, sometimes after surgical intervention.

Oral medications. Widely used, either in monotherapy, or more frequently for severe spasticity in combination, oral medications remain the treatment of choice in most patients with spasticity. The quantity and quality of available evidence regarding the efficacy of these medications in the treatment of spasticity is often limited, and many of them are used off-label in this indication. Among their potential side effects, CNS sedation and weakness (either by direct effect or via unmasking of underlying weakness) are the most common. Baclofen is a structural analog of GABA, which binds to pre- and postsynaptic GABA-B receptors. Rapidly absorbed after oral administration, baclofen has a mean half-life of 3.5 hours, and for the most part is directly excreted by the kidney. CNS depression is the main side effect (sedation, drowsiness, fatigue, confusion, and dizziness). Potential risks of treatment include withdrawal syndrome (severe muscle stiffness, paresthesias, hallucinations, confusion, fever, and seizures) after abrupt discontinuation, and overdose (hypotonia, respiratory depression, hypotension, and coma). Both situations, although reversible, require prompt intervention.

Tizanidine is a central α-2-adrenergic receptor agonist. It is well absorbed and undergoes extensive first-pass hepatic metabolism. Monitoring of liver function is recommended. Hypotension is another significant potential adverse effect of this medication. Association with antihypertensive agents should be avoided or done with caution due to the risk of potentiation.

In addition to these two first-line oral medications, benzodiazepines, dantrolene sodium, gabapentin,

clonidine, and more rarely cyproheptadine may also be useful.

Local treatments. Local treatments are used to manage focal spasticity or focal consequences of diffuse spasticity. Local anesthetic agents have a short duration of action, but may be helpful to evaluate the potential benefit of longer-acting agents, or to facilitate rehabilitation. Chemical neurolysis with phenol, or less frequently ethyl alcohol, is still used on select targets (eg, obturator nerve to decrease adductor spasticity). Chemodenervation with botulinum toxin (BT) is increasingly popular, although it has not been approved by the FDA for the treatment of spasticity. Preparations of BT-A and BT-B are commercially available. Current guidelines in adults recommend injection of a maximum dose of 400 to 600 units per session, with a maximum volume per injection site of 0.5 to 1.0 mL, and a delay $\geq$3 months before reinjection, except in select situations.[8] These recommendations are designed to reduce the risk of development of clinical resistance due to antibody formation.

Neuro-orthopedic and neurosurgical interventions. Surgical treatments, such as tendon lengthening, tendon transfer, neurectomy (eg, obturator neurectomy for adductor spasticity), and intramuscular lengthening may be helpful in conjunction with rehabilitation for fighting contractures from spasticity. However, if spasticity is intractable, the risk of recurrent contractures is high.

Destructive neurosurgical interventions (such as cordectomy and myelotomy) have generally been abandoned, with the notable exception of selective posterior rhizotomy, which aims at decreasing afferent signals to the spinal cord, and is still used with success, particularly in cerebral palsy.[9]

IT therapy. Intrathecal baclofen (ITB) therapy has been approved by the FDA for the treatment of severe spasticity of spinal or cerebral origin refractory to oral antispastic medications, or when oral medications are not tolerated. The IT route of administration achieves effective cerebrospinal fluid (CSF) concentrations with much lower doses of baclofen, resulting in plasma concentrations 100 times lower than those seen with oral administration, a lumbar-cisternal concentration gradient estimated at 4:1, and as a consequence a reduced incidence of CNS sedation. Published data, for the most part either retrospective or pre/postobservational prospective studies, show that ITB achieves a long-term control of severe spasticity in various pathologic conditions. Contraindications to ITB therapy are few and include known hypersensitivity to baclofen, active infection at the time of screening injection or surgery, and all severe concomitant pathologic conditions that would preclude surgery. Potentially life-threatening complications of ITB therapy include overdosing (most commonly due to procedural errors) and withdrawal syndrome (due to procedural errors, missed refill with empty reservoir, and system malfunction). Other complications (eg, infections, wound dehiscence, seroma, and CSF leak) and causes of catheter (eg, fracture, subdural migration, disconnection from the pump, occlusion) or pump (eg, rotor lock, battery failure) malfunctions are not specific to ITB.

Opiates and clonidine have also been used intrathecally to treat intractable spasticity in multiple sclerosis (MS), alone or more frequently in combination with baclofen.[10,11]

ITB Therapy for Spasticity in Practice

Patient selection. Patient selection is one of the most, if not the most, critical step in the ITB treatment algorithm. The patient should fit the criteria for severe spasticity, with documented failure of oral medications and rehabilitation, and spasticity of cerebral origin should be present for at least 1 year. Beyond this minimum set of formal requirements, many other factors are to be taken into consideration, such as the relative stability of the underlying condition, the absence of unrealistic expectations, and any foreseeable elements compromising the compliance with adjustments and refills (eg, cognitive deficits, lack of caregiver[s], or lack of reliable transportation).

Patient (and caregiver) education is very important, and ideally should rely on verbal individualized information as well as written documentation (to which the patient can refer at home), and if available other media (videotapes, CD-ROMs, websites). Critical information needs to be repeated often during the process.

Patient evaluation should be standardized as much as possible, to allow a better comparison between pre- and postsurgery status. Multidisciplinary evaluations are preferable, and most frequently involve physicians, nurses, and physical and occupational therapists, but may also include, as appropriate, psychologic, neuropsychologic, and social work assessments.

Test injection. Although some clinicians may believe that the effects of ITB are predictable enough with sufficient experience that they do not need a test injection to determine if the patient is a good candidate for ITB therapy, this procedure is essential to document a significant improvement and good tolerance of the medication and to allow the patient (and caregiver) to better anticipate the effect of a

baclofen pump and therefore to make a more informed decision. The dose injected usually varies between 25 and 100 μg, and vital signs, adverse effects, as well as the results of ITB are monitored during the same period. One may consider using lower doses (as low as 12.5 μg) for ambulatory patients to estimate whether good control of spasticity can be achieved without significant loss of function ("functional screening injection"). It may be necessary to perform several screening injections before reaching a final conclusion. Continuous infusion of baclofen via an external pump may be used to better mimic the effect of the pump, but requires a hospitalization and carries a higher risk of infection. This technique seems to be particularly helpful in patients with dystonia.

Surgery. Surgical techniques are not fundamentally different from other indications of IT therapy. Catheter tip placement is typically at the lower thoracic level, to achieve control of spasticity in the low back and lower extremities. Higher catheter placement can be considered when there is severe upper extremity spasticity, keeping in mind the risk of worsening of trunk weakness.

ITB management. Rate adjustments begin as early as the day after pump implantation, and may continue for several months. Published data suggest that significant rate changes occur mostly in the first 6 months.[12] The maximum interval between refills is currently limited to 3 months, due to concerns over the stability of the medication beyond this time period. Overall, troubleshooting follows the same rules as other IT therapies, after ruling out potential triggers for increased spasticity, exacerbation of the disease, and tolerance to baclofen.

Miscellaneous issues. Rehabilitation is important throughout the process, and will frequently be facilitated by the control of spasticity with ITB. Aggressive stretching with ITB (being careful not to compromise healing of the surgical wounds), will often allow satisfactory recovery of range of motion where fixed contractures were thought to be present. Patients may experience transient weakness after the surgery (thought to be related to the stress of surgery), and often will have to learn how to function differently without relying on spastic muscles. This is particularly true for ambulatory patients, who must be retrained to use a different, often more physiologic, gait pattern.

Other treatment modalities may be used concomitantly with ITB. Oral medications are tapered off whenever possible, and this may result in significant improvement of energy level, and even cognition. It may be necessary to keep oral medications, either to control spasticity in areas not covered by ITB (eg, upper extremities) or to be used as needed for breakthrough spasms. Local treatments (eg, botulinum toxin) can also be administered in conjunction with ITB. Finally, pain medications may be mixed with baclofen when there is a significant associated pain component.

ITB must be integrated into the global disease management plan. If ITB does not interfere significantly with most other disease-modifying treatments, some medications may increase the risk of complications from ITB (eg, the use of immunosuppressants may increase the risk of infections in the perioperative period). The compatibility of the device with diagnostic and monitoring paraclinical tests is also important (eg, MRI compatibility in multiple sclerosis).

Changes in bladder/bowel control have been reported with ITB, although this does not represent a primary indication. Improvement of bladder function has been reported in SCI patients treated with a combination of ITB and clonidine.[13]

Published Outcomes of ITB Therapy

The literature provides an increasing number of publications on the short- and long-term outcomes of ITB therapy. The results generally suggest that the treatment is effective in spasticity of spinal and cerebral origin, with a variable incidence of complications. Most studies, however, either lacked a control group, were placebo-controlled but with a small sample size or a short follow-up period, or included mixed patient populations. Moreover, most of the initial placebo-controlled trials have focused on measures of resistance to passive movement, spasm frequency, and/or range of motion, and did not include standardized evaluation of function or quality of life. More recent articles have tried to include a broader range of outcomes, larger and more homogeneous samples, and a longer duration of follow-up.

Spinal cord injury (SCI). SCI is the condition that has probably generated the greatest number of ITB-related publications, although most studies have reported on mixed samples of patients with spinal spasticity (mostly SCI and multiple sclerosis).[14-18] This is a concern, because of evident differences in the evolution of these conditions over time. However, more recent studies, including only SCI patients, show similar results.[19] Most articles report on "traditional" spasticity outcomes, such as Ashworth scores, spasm frequency, and pain. Gianino et al reported significant improvement of Sickness Impact

Profile scores, but not Quality of Life Index scores, between baseline and 1 year.[20]

Multiple sclerosis (MS). Traditionally, ITB has been used mostly in nonambulatory MS patients with severe spasms. Prospective and retrospective studies have demonstrated that ITB provides relief of discomfort and pain related to spasticity, greater ease of care, improved posture, and improved ability to transfer.[21,22] Ambulatory MS patients have been considered more frequently for ITB therapy.[23,24] The risk of loss of function from increased lower extremity weakness, the uncertainty regarding the progression of disease over time, and the effect of ITB in this changing clinical picture all require very careful patient selection and testing procedures. However, at this stage of the disease, ITB has a larger potential impact in terms of disability, handicap, and quality of life in these patients who already are struggling with their spasticity and have difficulty conciliating the side effects of oral medications with the demands of their activities. There is a need for validated functional outcomes measures for this population. The newly developed Multiple Sclerosis Functional Composite (consisting of the timed 25-foot walk, nine-hole peg test, and PASAT) could be more helpful than the traditional Expanded Disability Status Scale, which is known for its lack of sensitivity to change in this range of disability. Interestingly, an increase in upper extremity MEP amplitude was reported in a sample of 11 patients with severe spastic quadriparesis from MS treated with ITB (compared with pre-ITB testing), but the investigators did not indicate whether this was correlated with changes in upper extremity spasticity, strength, or function.[25]

Brain injury. Meythaler et al[26] investigated 17 patients with spasticity and/or dystonia after traumatic brain injury (TBI), and reported improvement of traditional spasticity parameters up to 1 year after baclofen pump implantation. Becker et al[27] also reported positive results of ITB in 18 patients with anoxic or traumatic brain injury. Recent data suggest that ITB is beneficial in the early stages after brain injury,[28] challenging the requirement of a 1-year interval between the injury and the onset of therapy. Several studies have shown a positive effect of ITB on severe dysautonomia after brain injury.[28-30] Mixed results for ambulation were reported on a small sample (n = 3) of traumatic brain injury patients.[27]

Stroke. There is limited literature on the use of ITB in stroke. A recent double-blind, placebo-controlled crossover study in 21 stroke patients demonstrated significant improvement of spasticity measures after bolus injection and after up to 12 months of continuous ITB infusion.[31]

Cerebral palsy (CP). Murphy et al reported significant improvement of Ashworth scores in the lower and upper extremities in 23 children with CP, and identified factors associated with increased risk of complications,[32] confirming results from earlier studies.[33-35] Significant benefit was also demonstrated in adolescents and adults with CP.[36] Long-term improvement of generalized dystonia due to CP was reported in patients receiving continuous infusion of ITB, with improvement of ease of care and quality of life, but higher doses were required compared with reports on patients with pure spasticity.[37]

Cost-effectiveness and complications. A cost analysis study conducted in The Netherlands showed that most of the costs of ITB therapy were related to the surgery and initial hospitalization, whereas cost savings came from discontinuation of oral medications, preserved ability to work, and decreased nursing home expenses.[38] A Canadian cost-effectiveness study demonstrated cost savings related to reduced hospitalizations in the first 2 years after baclofen pump implantation (compared with 2 years before surgery).[18] Nielsen et al reported a need for continued increase in ITB dose in a subgroup of MS patients within a mixed population of 79 patients,[39] contradicting results from other studies demonstrating that ITB doses were overall stable after 6 months.[12]

Many publications have reported on the frequency of adverse effects and complications with ITB therapy, with variable results, and different methodologies. In a recent survey of 40 centers (936 pump placements),[21] the most common side effects after screening for intrathecal injection of baclofen were nausea/vomiting, sedation, hypotension, and urinary retention. The most common complications during hospitalization after pump implantation were CSF collection, constipation, headache, and CSF leak. The most frequent long-term complication was infection, which was also the most common reason for early pump replacement. The catheter had to be replaced due to malfunction in 7% of cases.

Conclusions

Overall, intrathecal baclofen therapy is an effective treatment for severe spasticity of spinal and cerebral origin. However, it also involves higher risks and costs than other therapeutic options for spasticity. Therefore, in clinical practice, thorough patient evaluation and education by a multidisciplinary team, careful treatment planning, minimization of perisurgical risks, and thorough management are keys to the success of an ITB program. Further research is needed on large samples of patients using rigorous method-

ology, including functional and quality-of-life outcomes, to capture the full spectrum of the treatment effect and to better identify predictive factors. Cost-effectiveness studies should take into account all the costs associated with severe spasticity, including professional and nonprofessional caregiving, medical complications imputable to spasticity, lost productivity, and decreased quality of life.

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