Spasticity after Spinal Cord Injury Part 2- Treatment

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Abstract

Spasticity is a common complication after spinal cord injury (SCI) within the upper motor neuron syndrome. We describe it in 2 parts: in the first one (Part 1) the pathophysiology, clinical features and assessment are shown, and in this part (Part 2) its treatment will be considered.

Once it has been decided to treat spasticity, the treatment is based on starting with simpler and less problematic activities, and increasing in complexity the procedures against spasticity. The possibilities of therapy with its characteristics are described: control of triggering factors, positioning, physical modalities (stretching, muscle strengthening, cold, splinting/ orthoses, electrical stimulation, robotic devices), oral medication (baclofen, diazepam, clonazepam, tizanidine, clonidine, and cannabinoids), intrathecal baclofen, local injections (phenol, botulinum toxin) or surgical interventions.

In order to assess the effectiveness of the different applied treatments we must measure outcomes. A management protocol is proposed for the spasticity of the SCI patient.

INTRODUCTION

Spasticity is one of the most frequent complications after spinal cord injury (SCI) and occurs in approximately 65% of the cases [1]. In this part the treatment of spasticity after SCI will be described, with its indications and modalities, while pathophysiology, clinical features and assessment of spasticity are shown in part 1.

Indications for treatment

The presence of spasticity in SCI patients does not necessarily indicate the need for treatment, because sometimes spasticity may increase stability in sitting and standing, facilitate the performance of some activities of daily living and transfers, increase muscle bulk and increase venous return [1-3], and even up to 40% of SCI people have reported spasticity as helpful in their lives [4].

For these reasons an objective measure (such as the intensity of the tone) cannot be used as a reference to decide whether or not spasticity is treated. The management of spasticity must be based on achieving a balance between positive and negative effects of spasticity on the patient [1], and then treatment is indicated for preventing contractures and loss of range of movement, reducing pain, easing positioning, skin ulcers treatment and hygiene, and facilitating activities of daily living (ADL) and transfers that could be hampered by spasticity [1,2,5].

Modalities of Treatment of Spasticity after Spinal Cord Injury

Since spasticity can change even on the same day and that a completely eradicating treatment is not possible, education becomes the centre of any management plan [2,5]. The patient must learn about spasticity, its clinical features and consequences, and how they can help themselves to manage and prevent symptoms, starting with controlling exacerbating factors [5].

Control of triggering factors: The first factor is to correct noxious stimuli; although those factors alone are not likely to provoke spasticity, they can always be considered when spasticity features appear or worsen [2,6]. So, positioning must be considered, neurogenic detrusor over activity, altered skin conditions (ingrown nails, pressure ulcers) or constipation must be treated, and pain, bladder infections or even tight clothing must be avoided [6].

Positioning: Since spasticity worsening (immediate or prolonged) can be due to different postures, positioning acquires a leading role within the treatment of spasticity, and it is based on improving alignment and symmetry, promoting relaxation of muscle tone and improving function [7], all this to avoid postural stimuli on spasticity and to maintain the length of the muscles [7-9]. The most frequent stimulus for spasticity in SCI is the extension of the hip (from flexion 20 degrees up to neutral position), and therefore we must be careful with the supine position and the transitions or transfers to supine position (wheelchair to bed) [6,7]. Sitting is the most adequate position; suggested positioning in wheelchair includes firm seat and back, knees and ankles at 90-degree angles and minimal dump of seat keeping anterior to posterior seat angle relatively level [10]. When SCI patient goes to bed, side lying can be a good posture, with flexion of the hip and knee on the uppermost side and mild flexion of the hip and...
knee on the lowermost side [2,7]. The use of tilt table or standing frame is supposed to help in spasticity treatment by providing prolonged stretch [2,11]. The treatment of pressure ulcers may interfere with proper positioning by trying to leave the ulcerated areas unsupported [12].

**Physical modalities:** Physical therapies are often considered the mainstay of treatment for spasticity and above all stretching [2,13], but the post effect of all of them is too short to allow a sufficient improvement [14]. Most of physical modalities are based in stretching reflex depletion due to prolongation of the stimulus (stretching, cold), and thus Golgi reflex stimulation with its subsequent muscle relaxation [15,16]. They are considered the first line of treatment for spasticity in SCI, as well as when the association of other treatments such as drugs starts [1,17].

**Stretching:** Prolonged stretch of a spastic muscle may inhibit that muscle by adapting of the intrafusal fibers to the increased extrafusal length; stretch must be maintained for at least 1 minute and ideally for 15 minutes to achieve muscle relaxation and increase in passive and active ranges of motion [2,16]. Techniques may vary by duration, velocity and intensity of stretch; the most frequent are self-stretching, casting or splinting, stretching within a physical therapy protocol and other devices [1,16]. There is no evidence for a specific mode, duration of the effect does not last more than 6 hours [1,9,18].

**Muscle strengthening:** This method is not used to treat spasticity but to treat its consequences, since as the strength of the non-spastic muscle increases, it is less difficult to move with the interference of the spastic antagonist muscle [1,8].

**Cold/ Heat application:** Cold acts by depletion of the stretch reflex but also can cause slowing of nerve conduction, decrease in activity of cutaneous receptors and alterations of Central Nervous System (CNS) excitability [10,18]. The effect usually lasts less than an hour so it can be used before other therapies [1].

**Splinting/ Orthoses:** Orthotic devices can be used for enabling long-term stretch but their use is very questioned [18]. Among them, splinting is preferred well than casting because the former allow a monitoring and treatment of the skin to avoid pressure ulcers so frequent in SCI [2,16]. Orthoses can only be used if spasticity is mild or after another treatment (e.g., botulinum toxin) that causes a previous relaxation to not elicit spasms [1,10].

**Electrical stimulation:** Application of tetanic contractions at high frequencies (> 2500 Hz) or transcutaneous electrical nerve stimulation (TENS) can be used because repetitive tetanic stimulation may fatigue the spastic muscle, but the benefits are short-term, and even long-term use of electrical stimulation has been reported to increase spasticity, especially in those with incomplete SCI [2,16,19]. Functional electric stimulation (FES) can be used for strengthening of antagonist muscles.

**Robotic devices:** The decrease of spasticity is linked with the functional improvement in SCI patient, both by prolonged stretching and by the strengthening of the antagonist muscles. These effects are reported in robot assisted therapy for upper and lower limbs [1,20,21].

**Other therapies:** Long-term vibration training may initiate the return of H-reflex paired-pulse depression in individuals with chronic, complete SCI [22]. Passive cycling has been proposed as a treatment for strengthening weak muscles because it could elicit sensory inputs to activate cortical structures and induce cortical plasticity changes leading to improved lower limb motor performance, but in human studies has failed to demonstrate efficacy [23]. Kinesio-taping is often used but is supported by no evidence [24]. Other proposed treatments are weight-bearing, hydrotherapy or hippo therapy [1,2,16].

**Oral medications:** Per oral medication is the first-line choice for general, regional and focal spasticity in SCI people [25]. However, there is no drug that is effective in all the patients, nor has sufficient evidence because most of the studies on spasticity do not include SCI [1,9,26]. Despite of this limited effect, drugs are the most used therapy for being simple to administer [25]. Other problems are the frequent side effects of all these medications and the possibility of leaving a chronic treatment by the patient for lack of adherence [1,2,25,27]. Oral medications are considered to be much more effective in spasticity of spinal origin than in that of cerebral origin, in which the efficacy of oral drugs is marginal as best and accompanied by high levels of adverse reactions, according with stroke clinical guidelines [26,28,29]. Four oral drugs are approved by the U.S. Food and Drug Administration for the treatment of spasticity: baclofen, diazepam, tizanidine and dantrolene sodium [9], although the latter has been forbidden or not authorized in many countries because of its peculiar adverse effects [30], and there is only reported significant efficacy for 2 drugs: baclofen and tizanidine [26].

**Baclofen:** It is considered the gold standard drug in SCI because it acts on receptors in the spinal cord, and for that it is the most widely used medication [1,9,31]. Gammabutyric acid (GABA) is an inhibitory neurotransmitter that acts in short interneurons in the CNS [32], and baclofen is a structural analogue of GABA and an agonist of GABAA receptors that acts binding pre and post synaptically to those receptors in spinal cord inhibiting monosynaptic and polysynaptic reflexes [31,33]. Although there is only one trial with only 6 SCI patients that compared oral baclofen with placebo [26,34], baclofen has been reported to be effective for reducing spasticity (particularly spasms) [31,35], but it may have negative effects on abilities for walking or performance of ADL and weaken muscle strength [31], and there are patients that may lose those abilities especially in elderly patients and bigger doses [36]. Baclofen has been shown to be safe and effective for long-term use [9]. Start dosage can be 15 mg/day divided in 3 doses and titration may be 15 mg each 4-7 day [31]; in older patients or with pluripathology the titration should be slower [31], and in children dosage starts with 2.5 mg/day to a maximum dose of 30 mg/day in children 2 to 7 years and 60 mg/day in children over 7 [37]. Adverse events seem to be dose-related and tend to disappear when doses are reduced, adverse effects are more likely to appear at oral doses ≥ 60 mg/day and 90 mg/day is reported as the maximum dose from which there is no greater improvement but more side effects [38]. The most common side effects are sedation, fatigue and drowsiness, other effects found are muscle weakness, confusion, dizziness, headache, hypotension, confusion or constipation [2,31]. A
particular caution is recommended in elderly people, epileptic patients and severe brain injured patients, and patients receiving baclofen should have liver function tests [14].

**Diazepam:** Presynaptic inhibition in the spinal cord is achieved by the increase of chloride conductance after binding of diazepam to GABA receptors. Diazepam has been the first drug studied against spasticity and its efficacy has been reported but as an adjunct to baclofen [31]. Like all benzodiazepines, diazepam is usually reported as being most effective in the treatment of hyperactive reflexes and painful spasms in SCI patients (dynamic component of spasticity) [1,31,39]. Single 5mg doses at night may be effective for nocturnal symptoms [31]. In children start dosage is 0.1-0.2 mg/kg/day, also usually a single night dose [37,40]. Adverse effects include sedation and cognitive impairment, and there is a potential for dependence. A withdrawal syndrome is associated with the benzodiazepines and abrupt withdrawal of diazepam has been associated with seizures [31].

**Clonazepam:** It is another benzodiazepine; less sedation and lower risk for dependence are described [1]. Clonazepam is typically used for the reduction of (night-time) spasms [10,35]; start dose is 0.5 mg/day, but if spasms continue to predominate over hypertonia, the dose can be increased without exceeding 3 mg/day. Withdrawal syndrome can be more dangerous with clonazepam than diazepam.

**Dantrolene sodium:** It acts at the muscle tissue to weaken overexcited muscles, inhibiting muscle action potential-induced release of calcium from the sarcoplasmic reticulum to the active myosin fibers during contraction [1]. It is not commonly used because of muscle weakness.

**Tizanidine:** Tizanidine is an imidazole derivative and is a centrally acting α2-adrenergic agonist which inhibits the release of excitatory amino acids in spinal interneuron’s [31]. In placebo-controlled trials, tizanidine has been shown to reduce muscle tone and frequency of muscle spasms in patients with SCI [41]; when compared with baclofen or diazepam in early trials, tizanidine demonstrated similar efficacy and better tolerability [31]. The effectiveness of tizanidine, usually considered as a second-line drug, is backed by the largest study [26,42]. The most common adverse effects are sedation, drowsiness, hypotension, dizziness, xerostomia and fatigue, liver function tests should be checked [1,31]. Treatment is initiated at 4 mg/day, increasing every 3 days by 2 to 4 mg/day; the total dosage should not exceed 36 mg/day in 3 divided doses [31]. In children, start dose is 2 mg/day, the total dosage should not exceed 9 mg/day (children 2-7 years) or 12 mg/day (children 7-12 years old) [37,40].

**Clonidine:** It is also a centrally acting α2-adrenergic agonist, and it can act spinally to reduce spasticity inhibiting sensory afferents, thereby suppressing spinal polysynaptic reflexes [1]. Clonidine is rarely used as a single agent in the treatment of spasticity; it has shown modest benefit as a supplement to baclofen [43]. Adverse effects include bradycardia, dry mouth, drowsiness, constipation, dizziness and depression, and above all hypotension, therefore it is not recommended for use in patients with cervical SCI, in whom baseline blood pressure is usually low [31].

**Cannabinoids:** THC (tetrahydrocannabinol) or mucosal spray is indicated for symptom improvement in adult patients with moderate to severe multiple sclerosis spasticity who has not responded adequately to other antispasticity medication [44]. The antispastic effect in SCI may be due to inhibition of polysynaptic reflexes [35]. It has been used in patients who did not respond to baclofen [45].

**Other oral drugs:** Gabapentin is structurally similar to GABA and has been used in multiple sclerosis spasticity [31]. Cyproheptadine is histamine and a serotonin antagonist that may reduce spasticity neutralizing the spinal and supraspinal serotoninergic excitatory inputs [1].

**Intrathecal drugs:** When spasticity is generalized, oral agents alone may not be enough for reducing spasticity and intolerable doses may be needed; in these cases we can deliver medication directly into the CNS with an intrathecal pump [2]. Baclofen is the most frequently used in intrathecal pumps, and has been studied for its use in SCI patients [46]. A programmable pump is implanted into the abdomen, from where a catheter conveys the baclofen into the intrathecal space, usually at the lumbar level since there is greater concentration of GABA receptors in the lumbar spinal cord [5]. The dose and flow rate of baclofen are individualized through external computer communication with a computer chip within the pump [10]. Effectiveness is much greater when spasticity is regional and affects to lower limbs [23] describing only 25% of antispastic effect over upper limbs [47], this has been attributed to catheter location usually below T10 level, but may treat also upper limbs if the catheter is placed mid-thoracic [48]. Prior to implantation of the pump, all candidates undergo a trial via lumbar puncture, with a dose of 50 µg of baclofen; tone and spasms are measured each 2 hours with Modified Ashworth Scale and Penn Spasm Frequency, and if result is positive, there is a 8 days period to gradually withdraw oral antispasmodic medication and then increase the dose of baclofen in the pump up to the optimum dose (average is 400-500 µg/day), which is kept refilling the reservoir pump at regular intervals (3-6 months) [2,25,31]. Most adverse effects tend to occur during the titration phase and include drowsiness, headache, nausea, weakness, and hypotension, other complications may be due to mechanical problems (dislodgment, disconnection, kinking, blockage), pump failure or infection [31]. Any interruption of intrathecal baclofen delivery may result in a severe baclofen withdrawal syndrome that is usually characterized by a sudden increase of spasticity, pruritus, hyperthermia, autonomic dysregulation, epileptic seizures, coma, rhabdomyolysis, disseminated intravascular coagulation, and multisystem organ failure [25,31,49]. Other drugs used via intrathecal for spasticity in SCI are clonidine, morphine or phenol [31,50].

**Local injections:** They are used when distribution of spasticity is focal, so their Indications in SCI are somewhat limited by the generalized nature of spasticity but are described in certain cases in which spasticity is focal, especially in ASIA C and D spinal cord injuries [5,51,52].

**Phenol:** Chemical neurolysis results in destruction of neural tissue by protein coagulation and is considered irreversible; injections can be targeted at peripheral nerves or motor points [5]. Despite of these factors it has been used in SCI people [53].
Botulinum toxin: Botulinum toxin serotype A (BoNT/A) is produced by the Clostridium botulinum bacterium, and is a metalloprotease which, in nerve endings, proteolitically cleaves synaptosomal associated protein (SNAP-25) to inhibit the fusion of the synaptic vesicle with the presynaptic membrane of the axon terminal, and thus ultimately relax the muscle [54]. BoNT is a drug indicated in focal spasticity, and approved by a number of institutions (Spanish Medication Agency; US Food and Drug Administration) for treatment of spasticity due to neurologic diseases such as cerebral palsy or stroke [55]. Its indication in SCI has not yet been officially proposed and there is very little literature on its use [51]. The most extensive case series about BoNT/A used in SCI published to date was by Marciñak et al., which included 28 patients treated with BoNT/A (onabotulinum and abobotulinum), generally in the flexors of the upper extremities and the antigravity muscles of the lower extremities [56]. Although spasticity is generalized, BoNT/A could be used in muscles that cause worse functional impairments such as hip adductors in SCI patients [55]. Adverse effects described are pain, infection, breaking at the point of infiltration, excessive weakness and development of antibodies [56].

Surgical Interventions

There are two modalities: treatment of the cause of spasticity and treatment of the consequences [1]. The first is not usually performed in SCI patients, but the latter may be useful in SCI acting over the muscle or the tendon to improve function, correct a deformity or for cosmetic reasons [18,57]. Orthopedic surgical techniques most frequent are tenotomies, tendon lengthening and tendon transfers [1,18].

Other treatments

The research of new therapies is based on the administration of new drugs [like fampridine (58)], or especially new strategies of neurorehabilitation [59]. Repetitive magnetic stimulation at the lumbar nerve roots has been reported to decrease lower limbs spasticity in SCI patients without important adverse effects [60]. Repetitive transcranial magnetic stimulation may be effective against spasticity in SCI patients, even more than against cerebral spasticity [61,62]. Pulsed radiofrequency applied to lumbosacral dorsal root ganglia has been also reported as effective against spasticity in SCI patients [63].

OUTCOME MEASURES

Changes in spasticity scales

Outcomes can be measured comparing the results after treatment with the previous situation [51]. The scale most frequently used to compare these results is Modified Ashworth Scale [2,46]. However, what is recommended is to use specific scales that assess spasticity as Patient-Reported Impact of Spasticity Measure or Spinal Cord Injury Spasticity Evaluation Tool [9].

Subjective assessment

It takes into account the opinion of the patient as well as that of therapists, nursing staff or caregivers [9]. To evaluate this opinion, we can use some model of scale type Patient Global Impression of Change (PGIC) that can be adapted whenever it includes an assessment as to improvement, worsening or no effect [64]. The typical PGIC scale consists of 7 points being point 4 when there is no effect, 5 to 7 different intensities of improvement (mild, quite or much), and 3 to 1 expresses worsening.

Tolerance and adverse events

Adverse effects and their importance should be collected, in case the treatment applied should be discontinued [51]. Tolerance can be assessed by the subjective opinion of the patient or a scale called Global Tolerance of Treatment Scale (Table 1) [65].

Other measures

It can be assessed whether the objectives set before the treatments have been achieved, by the scale Goal Attainment Scale that has been tested for SCI patients [66].

Management Protocol for Spasticity after Spinal Cord Injury

The treatment is based on starting with simpler and most conservative techniques, and increasing in complexity the procedures against spasticity [1,2]. There are no protocols or algorithms of management nowadays for spasticity [9], and it is only mentioned within the data set that must be evaluated among the musculoskeletal diseases of the spinal cord injured [67]. Most of the systematic reviews and meta-analysis have been performed on spasticity due to stroke or several mixed pathologies, so no evidence can be shown for any technique for SCI [9,26,68,69] A protocol for this treatment is proposed below with the steps to follow and an algorithm is shown in Figure 1.

Positioning and exercise: The first step is to promote an adequate positioning and educate the patient in the need to exercise daily; during acute in-patient phase this exercise will be performed in the context of physical therapy, and then in chronic phase perform only mobilizations or stretching as maintenance [5]. They are considered a preliminary step because although they do not cure the spasticity, they do prevent it from appearing or getting worse [1,2,51], and they are rules that should follow every SCI patient even without spasticity.

Control of triggering factors: Although it can also be applied to all patients, it can be considered as the first part of the treatment because it is the first factor to be taken into account when spasticity appears or is decompensated [1,8,51].

Baclofen: If spasticity must be treated, the first line drug is baclofen [31]. It starts with a dose of 15 mg/day (lower dosage for children, elderly people or concomitant drugs), and in 3-4 days it can be increased to 30 mg/day; we must wait 2 weeks to significantly evaluate the effect. If the response to treatment is

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<th>Table 1: Global Tolerance to Treatment Scale</th>
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<td>1. Excellent. No side-effects.</td>
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<tr>
<td>2. Good. There are minor side-effects, well tolerated by the patient.</td>
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<tr>
<td>3. Regular. Side effects cause problems for the patient, which can be resolved with a dose adjustment</td>
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<tr>
<td>4. Poor. Side effects are severe and require treatment discontinuation.</td>
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partial we increase to 45 mg/day and if it is complete the same dosage is maintained. If there is no response for 4 weeks we can go directly to point 3 by withdrawing baclofen.

**Second-line drugs**: After 3 weeks with baclofen at 15 mg/day and spasticity still with much functional interference, a second drug is added, and this depends on the spasticity features:

**Only phasic spasticity**: If the only symptom not controlled by baclofen is night spasms diazepam is added in a single dose. If there are spasms or other dynamic phenomena all day long then clonazepam is added.

**Predominance of hypertonia**: In general, the drugs preferred as adjuvants to baclofen are tizanidine or clonidine, considering that if the patient has a cervical SCI we only choose tizanidine.

**Third-line treatment**: If we are using 2 of the aforementioned drugs with a dose close to the maximum allowed or effective, we can add one of the others as third drug (for example, if we use baclofen and tizanidine we can associate diazepam). If one of the drugs mentioned above cannot be added as a third drug (elderly patients, prevention of adverse events), we can test other drugs with less recognized efficacy or focus on physical modalities (e.g., hydrotherapy).

**Focal spasticity**

If there are less than 4 muscle groups involved in spasticity, botulinum toxin is used. If spasticity is initially generalized but after administration of baclofen or others only focal spasticity persists, botulinum toxin is also indicated.

**Everything fails**

If we are using 3 or 4 oral drugs, we have all the exacerbating factors controlled, the patient performs physical activity, and despite all the spasticity is still intense or incapacitating, we will consider the intrathecal baclofen pump. In order to place the pump, the previous baclofen test must have been positive, there must be free intrathecal flow, the patient must be motivated and psychologically stable, and there must have been a minimum time of evolution of the lesion that in our center is 1 year.

**REFERENCES**


