Module 2: Nonsurgical Management of Spasticity

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Abstract

Spasticity management should be part of a well-coordinated and comprehensive rehabilitation program that is patient-centric and goal-specific. There are a variety of options available for the treatment of spasticity. A usual approach is starting with the least invasive treatment modalities initially and gradually increasing to more complex interventions as this is required. This curriculum considers oral antispasticity drugs in terms of mechanism of action, clinical use, efficacy, and adverse events. It also presents other treatment options, such as chemical neurolysis using phenol and alcohol and chemodenervation using botulinum toxin A (BoNT-A). Therapeutic intramuscular injections of BoNT-A require sound patient selection, accurate muscle selection, and precise localization. The common methods for achieving these are described. The importance of physiotherapy is explained, along with the necessity to combine treatment modalities to address spasticity and the various components of the upper motor neuron syndrome. Recognizing differences in various health-care systems across countries and regions, the authors aim to present various treatment options. While this section of the curriculum highlights the importance of an interdisciplinary effort in managing spasticity, it is understandable that not all treatment options are available uniformly. The challenge to clinicians is to make the most of the management options on hand to optimize outcomes.

Keywords: Spasticity-non-surgical treatment-antispasticity drugs-BoNT-A-nerve blocks

Learning Objectives

On completion of this module, the learner will be able to:

1. List nonsurgical treatment options in spasticity
2. Elucidate the mode of action, dosages, and side effects or oral antispasticity drugs
3. Explain when intrathecal or intramuscular drugs may be more appropriate
4. Describe how physical and pharmacological treatments should be combined for optimal outcome
5. Explain the use of nerve blocks in spasticity and to be able to compare phenol and BoNT-A nerve blocks
6. Spell out the main techniques of identifying muscles for injection and be able to demonstrate muscle identification
7. Define adjunctive therapies post-BoNT-A and understand the evidence base behind treatment regimens
8. Demonstrate BoNT-A injection techniques
9. Identify the health-care professionals who are needed to provide the combined skills for appropriate nonsurgical management of spasticity.

Access this article online

Quick Response Code:

Website: www.jisprm.org

DOI: 10.4103/2349-7904.347808

Spasticity Treatment Options

Many therapeutic interventions are used either alone or in combination in the management of spasticity. This Curriculum described nonsurgical treatments and provides an overview of physical and nonpharmacological modalities as well as pharmacological treatment modalities.

Nonsurgical treatment(s) should form the basis of management, although not all of these options may be available in all treatment centers.

Nonpharmacological and nonsurgical/nonorthopedic treatment should be the starting point of spasticity management and not disregarded, even if progression to pharmacological or surgical interventions follows [Figure 1].

Stand-alone pharmacological and surgical management is often not recommended; treatments should be used in combination with other therapeutic modalities encompassing an interdisciplinary rehabilitation approach.[2]

Spasticity management should be part of a wider rehabilitation program that is patient-centric and goal-specific. It should comprise multimodal treatment delivered as both generalized and focal interventions, and importantly, it should be remembered that spasticity treatment is a

How to cite this article: Reebye R, Balbert A, Bensmail D, Walker H, Wissel J, Deltombe T, Francisco GE. Module 2: Nonsurgical management of spasticity. J Int Soc Phys Rehabil Med 2022;5:S23-37.

dynamic process requiring constant re-evaluation and updating.

Physical and other nonpharmacological modalities

The role of physical and other nonpharmacological modalities in managing spasticity

Appropriate physiotherapy is central to the management of patients with spasticity, and the physiotherapy team should be an integral part of treatment planning from an early stage.

The role of physiotherapy includes, but is not limited to, early intervention to maintain muscle length, maintenance of joint alignment, prevention of secondary complications, strengthening of antagonist muscles, strengthening of proximal and axial muscles to improve central stability, and task-specific training.[3]

Despite its central role in rehabilitation (and possibly because it has been a long-standing treatment modality), there is actually a paucity of clinical trial data underpinning the use of physiotherapy. Similarly, a recent systematic review has concluded that there is a lack of high-quality evidence for many modalities. There is "moderate" evidence for electro-neuromuscular stimulation and acupuncture as an adjunct therapy to conventional care in stroke patients. Only "low-"quality evidence exists for rehabilitation programs targeting spasticity (e.g., induced movement therapy, stretching, dynamic elbow-splinting, occupational therapy) in stroke and other neurological conditions.[2] These authors concluded that further research is needed to judge the effect of nonpharmacological interventions with appropriate study designs, timing and intensity of modalities, and associate costs of these interventions. Yet, it should be noted that absence of strong research-based evidence does not mean that these treatment approaches do not contribute to the overall outcome of spasticity interventions.

Self-rehabilitation

Self-rehabilitation is a system of encouraging patients to be involved in their own rehabilitation by recording activities including daily self-care, use of devices and equipment, and socializing along with exercises and activities recommended by the health-care team.[4] Involvement can help patients feel that they still have some control over their own situation. A systematic and meta-analysis of randomized trials[5] showed similar results for Barthel index, Berg balance, and Fugl–Meyer scoring in home-based rehabilitation versus conventional rehabilitation, but the studies lacked spasticity outcome measures.

Another study,[6] considering home-based tele-supervising rehabilitation on physical function in stroke survivors, suggested that it could play a role in improving functional recovery in stroke survivors. To date, there has not been any published randomized control trials of BoNT-A + self-rehabilitation versus BoNT-A alone.

Splinting/taping/casting

Casting/taping/splinting all rely on elongation of the muscle.

Providing a prolonged stretch decreases motor neuron activity in spastic limbs and can decrease spasticity since the stretch leads to increased muscle fiber tension and length through an increase in the number of serial sarcomeres.[7]

Using this maintained low-load stretch, muscle tissues unfold and collagen fibers within the connective tissues undergo temporary re-alignment of which stimulates growth of the muscle.[8-10]

However, in muscles with increased tone, the shortening of muscles and connective tissues recurs unless the muscle length and stretch is maintained.[10]

Casting may be inhibitive or serial. Inhibitive casting consists of one application of a cast post injection, which is removed within 2 weeks to help decrease tone.[11]

Serial casting uses a series of progressive casts to increase muscle length using low load prolonged stretch to soft tissue.[7-9,12]

Casts can remain in place for between 5 and 10 days each and may be repeated 3–4 times in succession. If 15° from the neutral position of a joint is reached, then the casting can be stopped and an orthotic brace used to help keep the range of motion.

The spasticity patterns amenable to serial casting in the upper limb are flexed elbow, pronated forearm, and flexed wrist. In the lower limb, equinus foot and equinovarus foot may be treated. Casting has also been applied to knee flexion spasticity.

Transcutaneous electrical stimulation

The hypotheses for transcutaneous electrical stimulation (TENS) in reducing spasticity include:

- Modulation of excessive alpha motor neuron activity through dynorphin release
- Reduced corticomotor excitability – plasticity
- Modulation of reciprocal inhibition via 1a
- Increase in presynaptic inhibition via 1b

Of 6506 articles identified, 10 studies with 360 subjects were included in the systematic review by Marcolino *et al*.[13] In this review, it was shown that six studies demonstrated that TENS alone or as additional therapy was superior to placebo to reduce poststroke spasticity assessed by the modified Ashworth scale, especially in lower limbs (−0.58 [−0.82 to − 0.34] $P < 0.0001$, 5 studies); low-frequency TENS showed a slightly larger improvement than high-frequency, but without significant difference between subgroups.[13]

Extracorporeal shock wave therapy

The mechanism behind extracorporeal shock wave therapy (ECSWT) is unknown, but it does not seem to be related to a decrease in spinal excitability.[14] Several theories have been proposed to explain ECSWT:

- Nitrous oxide produced in response to ECSWT may have an effect on synaptic plasticity, and formation of neuromuscular junctions in the peripheral nervous system (PNS)
- Effects on neurotransmission at the neuromuscular junction
- Modulation of muscle rheology.

The effects last up to 12–16 weeks (but no study with longer follow-up has been conducted). When used alone, ECSWT can reduce spasticity in forearm and triceps following stroke.[15-17] Three sessions provided a longer effect (16 vs. 8–12 weeks) and better hand function–wrist control than one session.[16]

When used with BoNT-A, ECSWT compared with BoNT-A plus ES showed results in favor of ECSWT for MAS, spasm frequency scale, and pain (using a visual analog scale).[18]

Noninvasive neuromodulation

Two narrative reviews of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation as spasticity treatment have recently been published.[19,20] They reported that low-frequency rTMS over the unaffected hemispheres could be effective in the reduction of spasticity when applied with alone or with conventional therapies. The need for uniform, large, multicenter trials to confirm these findings was highlighted by the authors.

Robotics

Little evidence exists concerning the use of robotics in spasticity. A review of electro-mechanical and robot-assisted arm training has concluded that the quality of evidence is very low and studies show too much heterogeneity in intensity, duration, amount of training, type of treatment, and participant characteristics to make meaningful conclusions.[21]

Oral medications

Mechanism of action, indications, benefits, and potential adverse effects of oral spasmolytics

Generalized spasticity can be addressed with a variety of oral medications with differing mechanisms of action. The most commonly used oral agents include baclofen, tizanidine, benzodiazepines, and dantrolene sodium [Table 1].[22-24]

Baclofen is one of the more commonly used agents to treat generalized spasticity. It is a gamma-aminobutyric acid (GABA) analog that binds presynaptically to GABA-B receptors in the brain and spinal cord, thereby decreasing monosynaptic and polysynaptic reflex activity. The half-life is typically 2–6 h, and initial doses generally start at 5 mg BID to TID with slow uptitration as required and tolerated. The maximal daily dose is 80 mg/day; however, higher doses have been effective and well tolerated in certain populations including individuals with spinal cord injury.[25] Common side effects include sedation, ataxia, and muscle weakness. Abrupt withdrawal of this medication should be avoided as this can result in delirium, seizures, and hallucinations. Overdose of baclofen can cause altered mental status, respiratory distress, coma, and death.

Benzodiazepines may also be useful in the management of generalized spasticity and particularly spasticity with painful spasms. The most commonly used benzodiazepine is diazepam. It binds near the GABA-A receptor to assist the binding of GABA to the GABA-A receptor, thereby increasing presynaptic inhibition. Its half-life is 20–80 h. The typical starting doses are 2 mg twice daily or 5 mg if initially dosing at bedtime to assist with management of nocturnal symptoms. Doses can be uptitrated to maximize efficacy, with usual doses between 2 and 10 mg divided three to four times daily, up to a maximum of 30 mg per day. Higher doses may be used in individuals with spasticity due to spinal cord injury.

Common side effects include sedation, impaired cognition, weakness/incoordination, and respiratory depression/coma in overdose. The risk of addiction and dependence must be considered in those receiving high doses over a long period of time. Caution must be exercised when using diazepam in individuals with hepatic dysfunction as it is metabolized by the liver. This medication cannot be discontinued abruptly due to risk of withdrawal, which presents with symptoms such as anxiety, agitation, nausea, seizures, and death.[26] Other benzodiazepines such as clonazepam and ketazolam may be effective in certain populations.

Alpha blocking agents such as tizanidine and clonidine may also be effective in managing generalized spasticity. Tizanidine is a central alpha-2 receptor agonist which binds to alpha-2 receptors and prevents the presynaptic release of excitatory neurotransmitters; it may also enhance the release of inhibitory neurotransmitters. The half-life of tizanidine is 2–4 h, and starting doses are 2–4 mg doses initially administered at bedtime with gradual uptitration to twice or thrice daily dosing. Maximal daily dose is 36 mg/day. Common side effects include sedation, dizziness, hypotension, and dry mouth. It is important to note that tizanidine is available in capsule and/or tablet forms which are both equally absorbed on an empty stomach. However, when taken after a meal, the tablet is absorbed much faster, which may increase side effects or cause them to manifest quickly. Clonidine is another alpha-2 agonist that may be used to treat spasticity; however, it has a much greater effect on blood pressure and may result in more significant hypotension.

Dantrolene sodium is the only agent that acts peripherally at the level of the muscle to decrease spasticity. It blocks the release of calcium from the sarcoplasmic reticulum within the muscle, thereby decreasing the force of muscular contraction. The half-life is 15 h, and doses typically are started at 25–50 mg daily with gradual uptitration as needed to a maximal daily dose of 400 mg/day divided TID to QID. Common side effects include nausea, diarrhea, and weakness. Although less of an issue compared with the centrally acting spasticity agents, dantrolene can also cause cognitive side effects. Dantrolene may be hepatotoxic, particularly at high doses; therefore, liver function tests (LFTs) must be monitored.

Other options are also being investigated for the management of spasticity. Cannabis has gained popularity in recent years for the management of multiple medical issues including spasticity. D9-tetrahydrocannbinol (THC) and cannabidiol (CBD) are the active ingredients in marijuana. THC is a partial agonist to the CB1 and CB2 receptors in the central nervous system (CNS) and periphery which can provide analgesia, nausea, and muscle

Table 1: Oral antispasticity drugs

Mode of action	Dosing	Side effects
Baclofen		
Baclofen is a GABA analog that binds to presynaptic GABA-B receptors in the brain and spinal cord to decreased monosynaptic and polysnaptic reflexes Binding causes an influx of calcium into presynaptic terminals which decreases the release of excitatory neurotransmitters leading to decreased reflex activity Binding of baclofen to GABA-B receptors may also decrease gamma motor neuron activity, thereby decreasing muscle spindle activity	Half-life is 2-6 h Starting dose 5 mg BID to TID increase dose slowly with dose titration Package insert states maximal daily dose 80 mg/day, but higher doses are used in other neurological disorders (SCI)	Sedation, ataxia, altered mental status, hypotonia, constipation and muscle weakness are common side effects Abrupt cessation can cause withdrawal reactions resulting in seizures, hallucinations and potentially death
Benzodiazepines		
Diazepam (the most commonly used benzodiazepine) binds near the GABA-A receptor to potentiate GABA binding to the receptor, increasing presynaptic inhibition Other long-acting benzodiazepines such as clonazepam and ketazolam have also been used in treatment of spasticity	Diazepam: Half-life 20-80 h Starting dose 2 mg to 5 mg if given at bedtime, 2 mg if given during daytime to limit sedation Dose can be gradually titrated upward to a maximum dose of 40-60 mg/day	Sedation, impaired memory and attention, impaired motor coordination Overdose may cause respiratory depression
Tizanidine		
Tizanidine is a central alpha-2 receptor agonist Binding to alpha-2 receptors prevents the presynaptic release of the excitatory neurotransmitters glutamate and aspartate It may also enhance the release of the inhibitory neurotransmitter glycine	Half-life is 2-4 h Starting dose is 2-4 mg given initially daily at bedtime (QHS), with gradual increase by 2-4 mg every 2-4 days Maximal daily dose 36 mg/day	Sedation, dizziness, hypotension, dry mouth May cause elevated liver function tests. Patients should be monitored at baseline and 1, 3, 6 months Tizanidine is available in capsule or tablet, with equal absorption on empty stomach; however, when taken after a meal, the tablet is absorbed much faster which may increase side effect profile
Dantrolene		
Dantrolene is the only antispasticity agent that acts peripherally at the muscle to decrease spasticity by inhibiting ryanodine receptors It decreases the release of calcium from the sarcoplasmic reticulum within the muscle which decreases muscle contraction force	Half-life is 15 h Starting dose 25 mg per day with gradual upward titration every 5-q7 days to maximal dosage of 100 mg QID	Nausea, vomiting, diarrhea, dizziness, weakness. Fewer cognitive side effects than centrally acting spasticity medications May cause hepatotoxicity, particularly in high doses. Monitor liver function at baseline and intermittently
Less commonly used agent for non-CVA spasticity		
Clonidine		
Clonidine is an alpha-2 agonist	Dose: 0.05-0.2 mg BID orally, or 0.1-0.3 mg transdermally	Orthostasis, bradycardia, constipation, edema, drowsiness Clonidine has a more significant effect on blood pressure than tizanidine
Cyproheptadine		
Cyproheptadine is a histamine and serotonin antagonist Its antispasticity effects are thought to be due to neutralization of serotonergic excitatory input at spinal/supraspinal levels	Starting dose 4 mg QHS with dose increases of 4 mg every 3-4 days. Most common effective doses 16-24 mg/day	Sedation, dry mouth. May also stimulate appetite and cause weight gain
4-Aminopyridine		
4-Aminopyridine is a potassium channel blocker which restores conduction along focally damage axons by prolonging the duration of action potential along demyelinated axons	Half-life 3.5 h Maximal dose 10 mg BID	Dizziness, headaches, paresthesias, insomnia, nausea
Cannabinoids		
D9-THC and CBD are active ingredients in marijuana THC is partial agonist to the CB1 and CB2 receptors in CNS and periphery They provide analgesia, muscle relaxation, decrease nausea and stimulate appetite They have been shown to improve spasticity in MS models Synthetic formulations include pharmaceutically derived cannabinoids (nabilone and nabiximols)	Clinical use limited by availability, physician comfort with prescribing, and limited evidence for use in stroke population Potential concern that use of cannabis may increase risk for stroke[23]	Adverse psychological effects including anxiety, psychosis and panic attacks. Also noted to impair motor coordination and executive function, with long-lasting cognitive effects in chronic users[24]

Contd...

Table 1: Contd...

Mode of action	Dosing	Side effects
Canadian clinical practice guidelines recommend use of nabilone or nabiximols in individuals with spasticity due to MS or SCI that is refractory to standard treatments[22]		

THC: Tetrahydrocannabinol, CBD: Cannabidiol, GABA: Gamma-aminobutyric acid, CNS: Central nervous system, SCI: Spinal cord injury, QHS: Bedtime, QID: Four times a day, CVA: Cardiovascular accident, MS: Multiple sclerosis, BID: twice a day

relaxation and may improve spasticity in some individuals such as those with multiple sclerosis. The exact mechanism of action is not well understood; however, it is thought that binding of the cannabinoids to the CB-1 receptors may inhibit release of excitatory neurotransmitters such as glutamate and enhance the effects of the inhibitory neurotransmitter, GABA. In terms of dosing and administration, no specific recommended dosing regimen in the USA is available currently. In Europe, THC/CBD is available in an oromucosal spray Sativex® (approved and marketed in Germany, Italy, Spain, Belgium, Luxembourg, Norway, Denmark, Sweden, Iceland, Portugal, Poland, Austria, and Switzerland. Not yet available in France, Republic of Ireland, Finland, Czech Republic, Slovakia, and The Netherlands. For further information see: Our products gwpharm.co.uk). The recommendation is to identify responders with an initial 4-week trial with a subsequent 14-day self-titration phase to optimize dosage.[27] Adverse effects of cannabinoid use include anxiety, psychosis, and pain attacks. It may also impair motor function/coordination and have a negative impact on cognitive function.[24]

Less commonly used agents include cyproheptadine (histamine and serotonin antagonist); phenytoin, oxcarbazepine, levetiracetam, and lamotrigine (sodium channel blockers); gabapentin and pregabalin (calcium channel blockers); tolperisone and eperisone (combined sodium and calcium channel blockers); and 4-aminopyridine (potassium channel blocker). Further discussion of these agents is beyond the scope of this curriculum; however, it is important to recognize that these agents may be used for spasticity management in some situations.

Competency Assessment 1

The answers to the competency assessments can be found at the end of the module before the references.

1. What is an important role of physiotherapy in spasticity management?
   a. Immobilization to protect spastic muscles
   b. Teaching energy conservation techniques
   c. Strengthening distal muscles to improve core (spinal) stability
   d. Early intervention to maintain muscle length.
2. A common side effect of diazepam and other benzodiazepines is:
   a. Tachycardia
   b. Insomnia
   c. Cognitive dysfunction
   d. Urinary retention.
3. To minimize the risk of sedation and impaired cognition in a person with poststroke spasticity, what oral spasmolytic agent will be the best choice?
   a. Diazepam
   b. Dantrolene
   c. Baclofen
   d. Tizanidine.
4. Regarding the use of serial casting for spasticity, what is the indication to discontinue?
   a. The cast has been in place for 3 days
   b. Additional 10° from the neutral position of a joint was reached
   c. Severe and persistent pain in the casted limb
   d. Failure to gain additional 5° range of motion after maintaining the cast for 7 days on two consecutive applications.
5. The likely mechanism of action of cannabinoids in decreasing spasticity is:
   a. Inhibit release of GABA
   b. Inhibit release of glutamate
   c. Promote release of glutamate
   d. Promote release of serotonin.

Mechanism of action, indications, benefits, and potential adverse effects of botulinum toxins

BoNT blocks acetylcholine release at the motor endplate level and therefore exerts a paralyzing effect on muscles, so it will affect velocity-dependent increase in muscle tone, spasticity, clonus, spastic dystonia, and associated reactions and weakens residual voluntary muscle contraction (spastic paresis). Different subtypes of BoNT may vary in their exact mechanism of action. BoNT-A – the most commonly used in spasticity– once taken up into the presynaptic neuromuscular junction cleaves synaptosome-associated protein 25 required for fusion of neurotransmitter vesicles and thus transmitter release. BoNT-B cleaves a vesicle-associated membrane protein. (Since BoNT-B is not utilized as commonly as the other BoNT-A, subsequent discussion will focus on the latter.)

BoNT-A injections into the shorter of the co-contracting muscles will augment stretching activities and allow antagonistic coordination to be trained by repetitive training activities in the therapeutic window of BoNT-A action.

BoNTs are the treatment of choice for focal and multifocal symptoms of spastic movement disorder (positive symptoms of the upper motor neuron syndrome [UMNS]) as part of a multimodal approach to management. BoNT significantly decreases muscle tone, spastic dystonia, clonus, and spasms

from UMNS and improves passive functions such as reducing spasticity-associated pain, improves hygiene and passive motility of involved limbs, and reduces disfigurement and associated reactions. A single spastic muscle is rarely treated in isolation, and it is important that the individual spastic pattern of muscle under- and over-activity, at rest and while moving, is correctly understood by the evaluating physician and therapist so that all relevant muscles can be treated appropriately by the injector.

BoNT is very much a long-term and individualized treatment. By modifying the target muscles, the BoNT dose (per session, per muscle, and/or per injection site), the interval between treatments, and the number of target sites, focal and segmental BoNT treatment can be tailored to individual patient's symptoms. However, muscle selection and dosing are based on the clinical experience of the treating physician.[28]

Clinically detectable reduction in muscle tone or of voluntary muscle force is evident after 24–72 h, and maximal effect occurs within 10 days to 4 weeks and can last for up to 12–24 weeks and these timelines must be recognized and included in the management plan.

Differences between different botulinum toxin products

The available BoNT-A drugs are different and not interchangeable. The most important difference in BoNT drugs available refers to the serotype used. So far, only BoNT-A and BoNT-B are commercially available, whereas BoNT-C and BoNT-F have been tried in humans in studies in dystonia only.

All BoNT-A products contain the 150-kD neurotoxin with or without nontoxic accessory proteins (NAPs). BoNT-B product contains the toxin (molecular weight not reported) with NAPs. Comparing different toxin formulations is extremely difficult, since a number of variables will affect performance (including serotype, strain of *Clostridium botulinum*, diluent, mouse strain used to standardize the toxin content, protein content, and the ratio of active to inactive toxin).

Differences in potency depend mainly on the amount of active toxin available in each vial (which depends on the manufacturing process). This means that the amount toxin in a vial does not reflect the real potency. Moreover, the potency differences demonstrated in mice may not be directly translated to humans and to clinical practice.

The commonly used formulations of BoNT are onabotulinum toxin A (Botox® Allergan); abobotulinum toxin A (Dysport® Ipsen); incobotulinum toxin A (Xeomin® Merz); and rimabotulinum toxin B (Myobloc® Solstice neurosciences) [Table 2].[29]

In addition, there are other formulations that are licensed but not in use worldwide: neuronox/botulax/regenox (letibotulinum toxin A, Hugel Pharma, South Korea) and BTX-A/prosigne/lantox (Lanxhou Institute of Biological Products, China).

Dose equivalence

Dosages of the BoNT-A drugs that are licensed in European and North American countries for the treatment of spasticity are given in the Summary of Product Characteristics of each drug; however, the doses and muscles licensed for each drug vary between different countries.

Various studies have investigated the dosing equivalence between onabotulinum toxin A and incobotulinum toxin A. Results show a 1:1 equivalence in rodents[30] in healthy volunteers[31] and in blepharospasm.[32-34]

However, the conversion ratio of onabotulinum toxin A and abobotulinum toxin A is far more variable, ranging from 1:3 to 1:11. Most authors consider that 1:3 or lower is an appropriate ratio to use, although some of these studies were in cervical dystonia[35,36] or blepharospasm. The 1:3 ratio has been demonstrated in cervical dystonia[37] and in cerebral palsy.[38]

A randomized controlled trial suggests the dosing equivalence of onabotulinum toxin A and letibotulinum toxin A to be 1:1 in upper limb spasticity.[39]

Due to differences in properties of individual toxins and lack of supporting evidence, a definitive conversion ratio cannot be feasibly recommended.

Differences in diffusions between the products

The diffusion potential of BoNT is complex and not well understood. Generally, intramuscular BoNT has a small diffusion potential in humans; however, this could be a potential source of side effects. *In vitro* studies have shown no differences between onabotulinum toxin A, incobotulinum toxin A, and abobotulinum toxin A.[40] Animal studies have demonstrated some spread in adjacent muscles[41] and spread has also been noted in hemifacial spasm.[42] Rimabotulinum toxin B shows less spread than onabotulinum toxin A.[43]

Side effects: differences between products

All products licensed for spasticity treatment are well tolerated and associated with few adverse events across all regions injected for spasticity treatment. Local adverse effects (AEs) are caused by local diffusion of BoNT-A from the target muscle into adjacent muscles or tissues. Systemic AEs occur in tissues distant from the injection site and based upon BoNT-A transport within the lymphatic or blood circulation. Those symptoms would include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties.

The AEs associated with all BoNT-A preparations occur with a typical latency about 1 week after injection of the toxin. Severity and duration of local and systemic AEs depend on the local or total dose of the different products applied.

Most cases of generalized weakness (botulism-like syndrome) have been reported with abobotulinum toxin A.[44-46] These data have been confirmed by analyzing the FDA Adverse Event System Reporting Database.[47]

High doses

Clinical experience has shown that using higher doses than those recommended in the package insert can be beneficial for some patients.

Table 2: Summary of botulinum toxins formulations

	Botox®	Dysport®	Xeomin®	Botulax®	Myobloc®
Generic name	Onabotulinum toxin A	Abobotulinum toxin A	Incobotulinum toxin A	Leitobotulinum toxin A	Rimabotulinum toxin A
C. botulinum strain	Hall A-hyper	Hall A	Hall A (ATCC 3502)	CBCFC26	Bean
Toxin type	A1	A1	A1	A1	B1
MW (progenitor toxin complexes)	900 kD complex (yes)	MW not reported (yes)	150 kDa None	900 kDa complex (yes)	MW not reported (yes)
Pharmaceutical form	Vacuum-dried powder for reconstitution	Freeze-dried powder for reconstitution	Freeze-dried powder for reconstitution	Freeze-dried powder for reconstitution	Ready-to-use solution
Shelf life	2°C–8°C 36 months	2°C–8°C 24 months	Room temperature 36 months	2°C–8°C 24 months	2°C-8°C 24 months
pH	7.4	7.4	7.4	6.5±0.5	5.6
Excipients	In 100 U vial HAS 500 µg NaCl (09 mg/vial)	In 500 U vial HAS 125 µg Lactose (2.5 mg/vial)	In 100 U vial HAS 1000 µg Sucrose (4.7 mg/vial)	In 100 U vial HAS 500 µg NaCl 0.9 mg	HAS 500 µg Succinate 10 mM NaCl 100 mM
Unit/vial	100 U or 200 U	300 U or 500 U	50 U, 100 U or 200 U	50 U, 100 U or 200 U	2500 U/0.5 mL 5000 U/1 mL 10,000 U/2 mL
Protein load/vial	5 ng/100 U	4.35 ng/500 U	0.44 ng/100 U*	<5 ng/100 U	55 ng/2500 U
Clinical activity compared to Botox®	1	1:2i1:3	1	1	1:40-1:50

*Neurotoxin concentration measured by ELISA. Units are manufacturer specific and not interchangeable. ®Hugel Pharma website. HAS: Human serum albumin, ELISA: Enzyme-linked immunosorbent assay

Reports have considered higher doses using abobotulinum toxin A in 6 patients treated with 2000 IU;[48] using onabotulinum toxin A in 84 patients described in 3 case reports using up to 800 IU[49] and 2 case series using 700 IU and 900 IU; and using incobotulinum toxin A in 284 patients in 6 case series using up to 1200 IU[49] and one prospective trial using 800 IU.[50]

A recent review of high-dose use of BoNT-A[51] has concluded that while evidence is still insufficient to recommend high-dose use in clinic practice, for some patients, the benefits may be clinically acceptable.

Immunogenicity

There may be differences between toxins in the immunogenic potential. Antibodies can be produced that are against the NAPs or against the neurotoxin (mainly against the heavy chain). Antibodies directed against the NAPs do not prevent the neurotoxin's biological activity while antibodies directed against the neurotoxin may or may not prevent biological activity (neutralizing or nonneutralizing antibodies). The incidence of anti-BoNT antibodies is 0%–3% for BoNT-A and 10%–44% for BoNT B.[52-54]

Performing botulinum toxin chemodenervation

It is recommended that injection guidance is used to inject BoNT-A in the target muscles, especially in small and deep-seated muscles. Recommended injection guidance techniques include ultrasound, electrical stimulation, or electromyographic (EMG) guidance methods.

To induce an optimal uptake of the toxin following injection within muscles with diffuse endplate distribution, injected volume per muscle should be distributed in more injection sites and this is particularly important in larger muscles. However, in muscles with discrete endplate bands, the dose of toxin should be divided across this defined endplate region at one or two sites.

To optimize the uptake rate of BoNT-A, the injected muscles should be activated following injection, e.g., by electrical stimulation or by procedures such as stretching of the spastic muscles, to enhance SV2-receptor exposure and therefore the binding and consecutive uptake of the BoNT injected.

With respect to combination of different treatment approaches, BoNT-A could be used to open a so called "window of opportunity" or "therapeutic window" with less spastic muscle tone and less positive signs of the UMNS, allowing a better combination of neurorehabilitative treatment approaches and better re-establishment of antagonistic co-ordination. Reversibility of BoNT-A effects may lead to repeated treatment in postacute and chronic spastic paresis with muscle tone increase, muscle over-activity, spastic dystonia, and disturbed reciprocal inhibition but may perhaps modify the course of muscle over-activity in early poststroke intervention.

Adjunctive therapies when using toxins

Controlled studies in the postacute phase of stroke rehabilitation (less than 3 month following stroke) have shown that BoNT-A injected before spasticity becomes chronic facilitates lower doses; also, improvements in impairment and passive function level tend to be more pronounced and longer lasting.[55]

Three review articles consider the evidence for adjunctive treatments[56-58] and show that adjunctive therapies can be effective, although the evidence is not robust, since there is considerable heterogeneity in study design and low patient numbers.[56-58]

The adjunctive therapies evaluated in the Mills review include electrical stimulation (ES) (n = 8); taping (n = 4); casting (n = 2); stretching (n = 2), ECSWT (n = 1); physiotherapy

(*n* = 1); segmental muscle vibration (*n* = 1); dynamic splinting (*n* = 1); modified constraint-induced movement therapy (*n* = 1); and motorized arm ergonometer (*n* = 1). The authors conclude that while there is a high level of evidence to suggest that adjunctive therapies may improve outcome, no results have been confirmed by independent replication and all interventions would benefit from further study.[57]

Comparisons between BoNT-A plus different adjunctive mechanisms[57] show that there is Level 1 evidence for casting being superior to taping and taping being superior to ES and stretching. Extra corporeal shock wave therapy (ESWT) is also superior to ES. Level 2 evidence suggests that immediate ES is superior to delayed ES and low-dose BoNT plus ES is equivalent to high-dose BoNT. Casting was also considered superior to taping by Picelli *et al*., but consensus about their most appropriate timing, duration, target, and material is lacking.[58] There is high-quality evidence that stretching does not have clinically important effects on joint mobility in people (with or without neurological conditions) if performed for less than 7 months.[58]

A study comparing BoNT-A treatment plus serial casting, taping, or stretching[59] in spastic equinus foot has shown that the modified Ashworth scale was improved more with casting than with stretching or taping. Similarly, ankle patient-reported outcome measures (PROM) showed superiority for casting over stretching at all time points and over taping at 90 days. The 6-min walk distance increased for casting and taping but not stretching.

It has been shown that ES increases synaptic activity which leads to increased BoNT uptake and increased mechanical spread of toxin in the short term.[60] Direct effects of ES on spasticity have been observed in both the short- and long-term. ES increases strength in antagonist muscles and BoNT-A decreases the tone in agonist muscles in the long term. However, the best protocol has not been defined.[58]

There is Level 1 evidence that ECSWT is better than ES for some postinjection outcomes including spasticity and pain.[58]

The evidence and a consensus statement for the use of adjunctive treatment are summarized in Table 3.

Case Study Mr. L

- A right-handed 59-year-old artist
- 2010: carotid dissection and subsequent stroke → left-sided hemiplegia
- Left upper > lower limb affected
- Flexor synergy upper limbs
- Extensor synergy lower limbs
- Left flexed elbow
- Left pronated forearm
- Left flexed wrist.

Patient goals and physician goals

1. To help decrease left forearm pronation and reduce left elbow flexion attitude to help his activities of daily living
2. To help with better arm position when walking
3. To help improve his walking speed and overall gait pattern
4. To enhance cosmetic appearance of arm position
5. To prevent contractures.

Case: injection of incobotulinum toxin A

- Incobotulinum A 200 U
  - Ultrasound-guided injection
- 60 units into pronator teres (PT), 40 units into pronator quadratus, 100 units into brachialis
  - Casting 10 days postinjection
  - Home stretching program 5 min per day
  - At 1 month, decrease in pronation spasticity
  - At 1 month, improvement of elbow extension
  - At 1 and 3 months, improvement in functional gait parameters as left arm less flexed at elbow [Figure 2].

Serial cast application

- 10 days postinjection
- Cast stretched to maximum stretch V1 value: 143°
- Arm was supinated in casting process
- Should perceive stretch but no pain
- Bony prominences are padded internally [Figure 3].

Gait videos

Pre- and post-casting videos [https://www.jisprm.org/articles/2022/5/5/images/IntJPhysRehabilMed_2022_5_5_23_347808_sm8.mp4] [https://www.jisprm.org/articles/2022/5/5/images/IntJPhysRehabilMed_2022_5_5_23_347808_sm9.mp4]

Competency Assessment 2

The answers to the competency assessments are given at the end of this module before the references. Each question has only one correct answer.

1. What is the mechanism of BoNT action?
   a. Increases acetylcholine release
   b. Blocks acetylcholine release
   c. Binds GABA-A receptors
   d. Binds α-2 receptors.
2. What are the indications for BoNT administration?
   a. Muscle weakness
   b. Muscle hyperactivity
   c. Muscle contractures
   d. Muscle rigidity.
3. When does the maximal effect of BoNT occur?
   a. After 24–72 h
   b. After 3–7 days
   c. Within 10 days to 4 weeks
   d. Within 2 months.
4. What are the most common side effects?
   a. Muscle weakness
   b. Muscle spasm
   c. Rash
   d. Nausea and vomiting.
5. What is a known beneficial effect of casting/taping/splinting?

Table 3: Summary of evidence and consensus statements for adjunctive treatment

Summary of evidence	Consensus statement
Casting/splinting/taping	
Selective groups of stroke survivors have benefited from casting/splinting/taping as an adjunctive therapy post-BoNT-A Current evidence lacks robust controlled research designs, large sample sizes for power calculation and sensitive outcome measures Critical need for high-evidence research on effect of casting/splinting/taping post-BoNT-A and long-term benefits in this population	Consider casting/splinting/taping as adjunctive therapy Main barriers to implementation: Access to casting, funding, experience, clinical time to monitor patient postcasting
ES	
Likely that ES provides some degree of additional effect physiological, and possibly, clinical benefit in conjunction with BoNT-A The ideal ES settings and protocol are also unclear (Hz, best time after injection to initiate stimulation, length and frequency of sessions), distinguish adjunct versus therapeutic The mandate for further research in this area is fairly high given the cost of BoNT-A and the intervention and the potential to augment the effect with an alternative, inexpensive and readily available modality	Consider ES as adjunctive therapy Main barriers to use: Lack of experience, availability of device, time constraints
ECSWT	
There is a need to establish the effects of repeated sessions, the mechanism of action, the muscle changes with ECSWT and the optimal sites and intensity for ECSWT use	Consider ECSWT as an adjunctive therapy to BoNT-A injections but practically difficult to implement Main barriers to implementation are cost, availability of device, lack of experience
Self-rehabilitation	
There is some evidence in the lower limb where repetitive task-oriented exercise focusing on balance control, transfers, gait, strengthening and stretching has been shown to be useful in improving gait in stroke Extrapolation of results from lower limb studies to upper limb may not always be appropriate	Recommend that patients are trained to follow a self-rehabilitation program for spasticity and poststroke recovery to supplement their clinician-administered physiotherapy
CIMT	
There is good evidence for the use of CIMT in poststroke rehabilitation	Good evidence for post stroke rehabilitation with CIMT Use for post stroke rehabilitation but studies lacking regards its use as adjunctive therapy to BoNT-A
Repetitive transcranial magnetic stimulation and transcranial direct current stimulation	
No evidence for BoNT-A + transcranial magnetic and transcranial direct current stimulation	Cannot recommend as adjunctive therapy post BoNT-A in PSS
Robotics	
No evidence for BoNT-A + robotics	Cannot recommend as adjunctive therapy post BoNT-A in PSS

CIMT: Constraint-induced movement therapy, ECSWT: Extracorporeal shock wave treatment, ES: Electrical stimulation, BoNT-A: Botulinum toxin A, PSS: Poststroke spasticity

a. Decreases muscle synergy
b. Increases spasticity
c. Elongates the muscles
d. Shortens the muscles.

Nerve blocks/chemoneurolysis

A nerve block is the application of a chemical substance to a nerve that will interfere temporarily or permanently with conduction along the nerve.

The use of nerve blocks for diagnosis and assessment purposes has been covered in Module 1 of this Supplement.

Mechanisms of action, indications, benefits, and potential adverse effects of phenol or alcohol nerve blocks

The therapeutic nerve block (TNB) consists of injection of a neurolytic drug (alcohol or phenol) on a motor nerve innervating a spastic muscle. The technique is the same as for the diagnostic nerve block (see Module 1 in this Supplement).

Phenol, alcohol, and local anesthetics are the most commonly used agents. Nerve blocks are intended to treat spasticity, hypertonicity, and other aspects of the UMN. Alcohol or ethanol at 50%–100% is commonly used for chemical neurolysis as well.

At concentrations of 4%–5%, phenol denatures the proteins in the myelin sheath and nerve axons. This is followed by an inflammatory reaction and Wallerian degeneration, but nerve regeneration can subsequently occur. Higher concentrations (~7%) can cause permanent nerve damage. The literature shows extreme variability in the duration of action of phenol, but this is partially due to the measurement tools used for assessment, the percent and volume of phenol, and the

individual injector's technique.[61] However, onset of action is usually always relatively rapid (<1 h).

Although systemic doses of 8.5 g of phenol are lethal (from cardiovascular failure and central nervous system dysfunction such as seizures), the doses used for neurolysis are way below this level (e.g., 20 mL of a 5% solution contains 1 g of phenol).

There are differing targets for alcohol or phenol nerve blocks. The site of the injection and the agents used can determine whether a nerve block is complete or affects only motor or sensory nerves. A phenol injection for a peripheral nerve block into a mixed nerve causes a total nerve block for 2–12 months (injection of a local anesthetic stops nerve conduction for a few hours). A motor point or end-plate block is injected into the motor branch of the nerve as it penetrates the muscle. The determination of whether to do a peripheral nerve versus motor point blocks is patient specific. If a patient has more global and severe spasticity, there may be need for a more longer lasting total nerve block. To minimize side effects of a total nerve block, such as painful dysesthesia, or when a patient has more functional movement, then a motor point block should be considered.

The injection site is determined by the number of muscles to be treated, the tolerance of the patient for a needle search, and the risk of needle search in different areas and dysesthesia if targeting mixed sensory and motor nerves (0.4%–32%; general consensus 15% for adults and 5% for children).[62,63]

The target of a nerve block injection is determined by the primary posture of the patient. For a patient with their shoulder in internal rotation, the physician would target the medial and lateral pectoral nerves. For a patient with a flexed elbow pattern, the musculocutaneous nerve would be the major target. For a spastic clenched hand, primarily, the median nerve would be targeted, though the ulnar is another consideration depending on the posture. For an adducted hip, the main targets would be the obturator nerve and the sciatic branch to the posterior adductor magnus. When a patient has an equinovarus foot, the tibial nerve would be the major target. Of the nerves listed above, there should be caution with the median and tibial nerves, as there is higher risk for dysesthesia in these sensory nerves.

The main clinical indications and target can be summarized as follows:

- Shoulder internal rotation — Pectoral major nerve
- Flexed elbow — Musculocutaneous nerve
- Spastic hand — Median and ulnar nerve (sensory risk +++)
- Adducted hip — Obturator nerve
- Equinovarus foot — Tibial nerve (sensory risk +++)

Some major comparisons between phenol nerve blocks and BoNT are shown in Table 4. Phenol is injected perineurally or intramuscularly at the motor points, while BoNT is injected intramuscularly. The maximal dosage of each substance is dependent on the clinical scenario. Maximal dosages of phenol would be less than 2 g (20 mL of 5%) and of BoNT would be 400 units within 3 months.

The main risks of phenol are pain of injection, chronic dysesthesia, and, in rare cases, permanent nerve palsy. Possible problems encountered with both phenol and alcohol injections can be bleeding, infection, and compartment syndrome due to the injection. (compartment syndrome occurs where the injection causes increased pressure in a compartment of the arm or leg due to the resistance of the surrounding fascia. This can damage muscle blood vessels or nerves or compromise the blood flow, leading to ischemia or necrosis).

Phenol or alcohol nerve blocks are often used in combination with BoNT-A. The indication for using phenol would be in larger or proximal muscle groups, especially when limited by the amount of BoNT-A in a patient with multiple muscle groups affected by spasticity. An example of this would be obturator nerve blocks to aid with hygiene of a patient who may have adductor tone and need to have diaper changers and fit comfortably in a wheelchair. Furthermore, blocks can be used when you do not have to be concerned with sensory integrity (i.e., complete spinal cord patients). BoNT-A can be injected in affected muscles that are accessible with intramuscular injections. It is also more often used to help with active function. Techniques for injection differ including stimulation of motor points for phenol or alcohol nerve blocks. The cost of the two is very different, with phenol or alcohol being low and BoNT-A being higher.

Nerve blocks can cause over-correction of the spasticity, strains or sprains, tissue atrophy, or temporary loss of useful motor function. Phenol injections can cause pain, temporary sensory loss, dysesthesias, painful nodules, swelling and inflammation, and hypotension.[61,64,65]

Performing alcohol or nerve blocks

A study has shown that obturator neurolysis with 5% aqueous phenol as guided by both ultrasound and electrical stimulation reduced hip adductor spasticity and improved hygiene scores and patient-centered outcomes measured by the GAS.[66] It was a double-blind placebo-controlled trial with a 9-month follow-up period (n = 26). Patients were randomized to two groups that received ultrasound and electrical stimulator-guided obturator nerve block using either 5% phenol in aqueous solution or saline.

In summary, chemodenervation with alcohol or phenol may be regarded as an old technique that provides transient treatment for focal spasticity. Nerve injection is preferred for a better effect, but sensory nerves should be avoided to reduce the risk of neuropathic pain. Chemodenervation can be combined with BoNT-A, especially when the maximal dose of BoNT-A is to be injected. Where a patient is likely to undergo subsequent nerve surgery, then treatment should be restricted to a single injection of alcohol or phenol since fibrosis could interfere with the surgical procedure.

Competency Assessment 3

The answers to these questions can be found at the end of this module before the references. There is only one correct answer for each question.

Table 4: Comparison of phenol and botulinum toxin A

	Phenol 5%	BoNT-A
Mechanism	Tissue destruction	Presynaptic block of ACh
	Circulatory damage	
Site of injection	Perineural or intramuscular damage	Intramuscular
Structure blocked	Sensory and motor nerve	NMJ
	MNJ	
Onset	<1 h	Days
Duration	Up to 36 months	3-6 months
Max dose/concentration	<1 g (10 mL of 5%)	400 IU within 3 months
Main risks	Pain of injection dysesthesia	No major risks but distal spread
	Permanent nerve palsy	
Indications	Proximal/large muscles	Muscles accessible with IM injection
	Sensory integrity not a concern	Sensory integrity indispensable
	Combination with BoNT	Active function
	Hygiene and comfort	
Techniques	Stimulation	Stimulation
	Motor point	End plate targeting
Cost	Low	High

BoNT: Botulinum toxins A, IM: Intramuscular, MNJ: Motor nerve junction, NMJ: neuromuscular junction

1. A common side effect of therapeutic nerve block using alcohol or phenol is:
   a. Sedation
   b. Drowsiness
   c. Dysesthesia
   d. Diarrhea.
2. What is a typical concentration of phenol for spasmolysis?
   a. 1%
   b. 3%
   c. 5%
   d. 7%.

Injection guidance

The role of guidance in identifying muscles and nerves for chemodenervation or neurolysis

BoNT-A injections may be localized using a number of techniques: anatomical localization, EMG guidance, electrical stimulation, or ultrasound. The use of all of these techniques concomitantly with anatomic localization can improve accuracy of muscle localization and may improve clinical outcomes.

Electromyography for injection guidance

An EMG detects the electrical nerve signals (potentials) generated by muscle cells when these cells are electrically or neurologically activated. EMG equipment consists of recording electrodes, preamplifiers (which are normally placed very close to the patient to avoid pick-up of electrical interference), amplifiers to provide the correct gain, calibration, and frequency characteristics, a display system (usually a cathode ray tube), a range of integrators and averagers partly to achieve some data compression (chart records may be very long and difficult to read), and a recording medium, which is often a photographic (fiber-optic) system.

EMG guidance is performed using an EMG machine, a hollow insulated monopolar needle electrode, and ground electrodes. The electrical activity detected by this electrode is displayed on the monitor (and may also be heard audibly through a speaker).

Using bony landmarks and palpation, the location of the target muscles should be established. The area near the motor endplate is targeted using electrode insertion sites as described in standard EMG texts.

Before the injection, the injector should palpate the target muscle and perform passive movement at the appropriate joint to initiate stretch on the target muscle which results in movement of the target muscle. Once the needle is inserted into the target muscle, the passive movement may be repeated, and the physician may observe movement of the needle or feel a tug on the needle.

Anatomical guidance

The accuracy of muscle localization with anatomical guidance was investigated in a cadaver study.[67] The accuracy of 121 physicians' performance in needle insertion into medial or lateral gastrocnemius of 30 cadaver limbs was evaluated. Once the needle was inserted, ink was injected into the target muscle. The limb was subsequently dissected by an orthopedic surgeon and an anatomist. Results showed that 43% of injections were placed appropriately; however, 37% were too deep and nearly 20% were too superficial. No difference in success rates were noted in physicians with >5 years injection experienced compared to novice injectors.

The accuracy of anatomical guidance has also been investigated in comparison with EMG and ES guidance. Molloy *et al*.[68] investigated needle placement with anatomic guidance verified with EMG. Only 37% of needle placement attempts were accurate using solely anatomical guidance.

Picelli *et al*.[69] investigated needle placement with anatomic guidance versus ES guidance verified with US in the medial and lateral gastrocnemius. ES guidance was noted to be

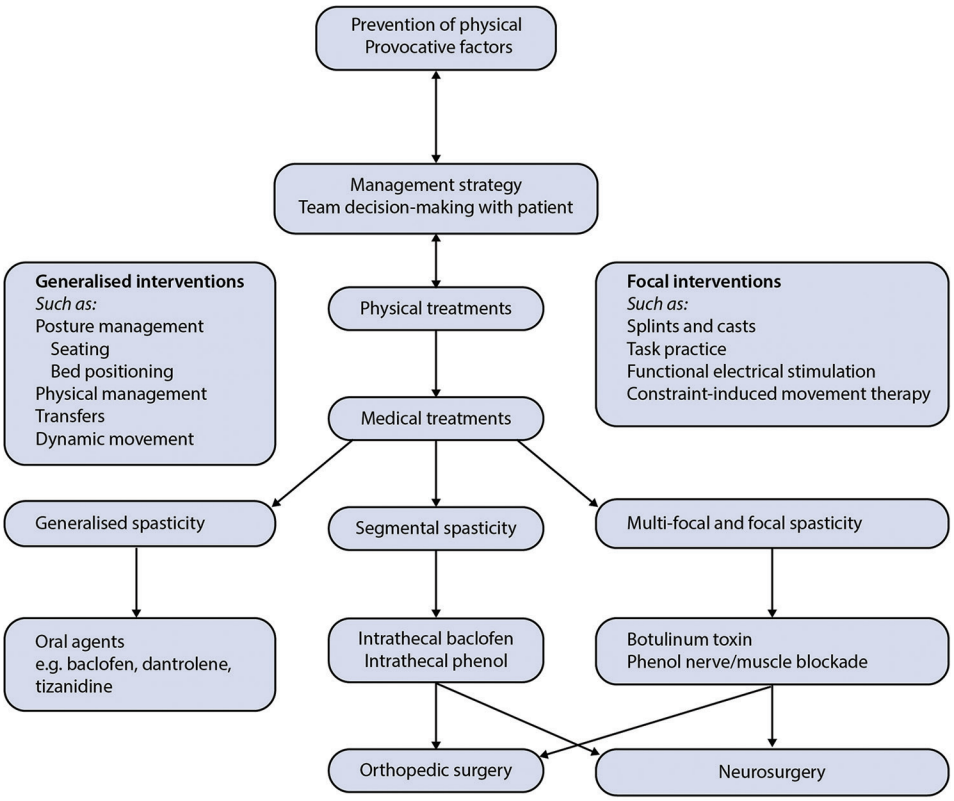

Figure 1: Spasticity treatment options[1]

superior in lateral gastrocnemius, but no difference was noted between groups for medial gastrocnemius.

Clinical outcomes using electromyography and electrical stimulation guidance

Mayer *et al*.[70] evaluated the efficacy of BoNT injections into spastic elbow flexors employing EMG or ES guidance. No significant differences were noted in the Ashworth scale, Tardieu spasticity angle, and surface EMG between groups.

Another study[71] compared the efficacy of BoNT injections in stroke patients with clenched fist or flexed wrist patterns of spasticity using anatomic, ES, or ultrasound (US) guidance. Both the ES and US guidance groups demonstrated improved MAS scores, Tardieu angle, and PROM postinjection compared to anatomic guidance; no significant difference was noted between ES and US guidance groups.

Ultrasonography for injection guidance

Anatomical guidance may be enhanced by the use of US to verify the needle placement before injections are performed.[72] In 41 adult patients with chronic CVA resulting in spastic flexed wrist and clenched fist, injections of BoNT-A were performed into the flexor carpi radialis (FCR), flexor carpi ulnaris, flexor digitorum superficialis (FDS), and flexor digitorum profundus. Once the needle was placed into target muscles, the location accuracy was confirmed with US before the toxin injection. If the needle was not placed into the targeted muscle, it was correctly repositioned under ultrasonographic guidance before injecting BoNT-A.

The overall accuracy of manual needle placement evaluated using ultrasonography was 51.2%. Accuracy was significantly higher for the finger flexors than for the wrist flexors (63.4% vs. 39.0%). The finger flexors were significantly thicker than the wrist flexors (mean 1.58 vs. 0.49 cm).

A similar study used US to evaluate accuracy of anatomical guidance in 18 adult patients with upper limb spasticity from brain injury or cardiovascular accident.[73] Accuracy of anatomic localization of flexor pollicis longus (FPL), FCR, PT, FDS evaluated using US. FDS injections were performed using surface landmark technique described by Bickerton *et al*.;[74] all other muscles used method described by Delagi and Perotto.[75]

The proposed injection site was marked on skin based upon anatomic localization. The optimal target sites then determined using US guidance. Optimal injections sites were found to be significantly different from proposed injections sites for FPL, PT, and FDS to digit 2.

In summary, both EMG and ES guidance are localization techniques that can be easily utilized to improve the accuracy of muscle localization and clinical outcomes of BoNT injections compared to anatomic guidance alone. The equipment was relatively inexpensive and easy to obtain, and EMG/ES guidance both have Current Procedural Terminology (CPT) codes covered by many insurance companies. Inexperienced injectors can often participate in preceptorship programs sponsored by BoNT pharmaceutical companies to gain experience in these techniques

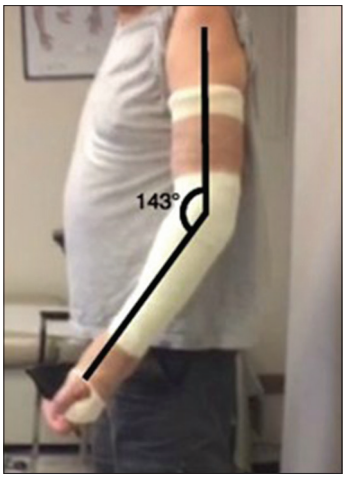

Figure 2: Patient image of serial cast application for Case Study Mr. L

Figure 3: Patient images of preinjection and postserial casting elbow angle for Case Study Mr. L

Competency Assessment 4

The answers to these questions can be found at the end of this module before the references.

1. In a study comparing ES with anatomic localization, in which muscle was ES found to be superior in correct needle placement?
   a. Gastrocnemius, medial head
   b. Gastrocnemius, lateral head
   c. Soleus
   d. Flexor digitorum longus.

Competency Assessment Answers

Competency Assessment 1

1. What is an important role of physiotherapy in spasticity management?
   a. Immobilization to protect spastic muscles
   b. Teaching energy conservation techniques
   c. Strengthening distal muscles to improve core (spinal) stability
   d. Early intervention to maintain muscle length.

The role of physiotherapy includes early intervention to maintain muscle length, maintenance of joint alignment, prevention of secondary complications, strengthening of antagonist muscles, strengthening of proximal muscles to improve central stability, task-specific training.

2. A common side effect of diazepam and other benzodiazepines is:
   a. Tachycardia
   b. Insomnia
   c. Cognitive dysfunction
   d. Urinary retention.

Common side effects of diazepam include sedation, impaired cognition, weakness/incoordination, and respiratory depression/coma in overdose.

3. To minimize the risk of sedation and impaired cognition in a person with post-stroke spasticity, what oral spasmolytic agent will be the best choice:
   a. Diazepam
   b. Dantrolene
   c. Baclofen
   d. Tizanidine.

Dantrolene sodium is the only agent that acts peripherally at the level of the muscle to decrease spasticity. Diazepam, baclofen, and tizanidine are known to cause drowsiness, sedation, and cognitive impairment.

4. Regarding the use of serial casting for spasticity, what is the indication to discontinue?
   a. The cast has been in place for 3 days
   b. Additional 10° from the neutral position of a joint was reached
   c. Severe and persistent pain in the casted limb
   d. Failure to gain additional 5° range of motion after maintaining the cast for 7 days on two consecutive applications.

If the cast causes pain, it should be immediately removed to allow closer inspection of the limb to determine the cause of pain.

5. The likely mechanism of action of cannabinoids in decreasing spasticity is:
   a. Inhibit release of GABA
   b. Inhibit release of glutamate
   c. Promote release of glutamate
   d. Promote release of serotonin.

Although the exact mechanism of action is not well understood; however, it is thought that binding of the cannabinoids to the CB-1 receptors may inhibit release of excitatory neurotransmitters such as glutamate, and enhance the effects of the inhibitory neurotransmitter, GABA. Increasing serotonin levels may increase neuromuscular hyperexcitability.

Competency Assessment 2

1. What is the mechanism of BoNT action?
   a. Increases acetylcholine release
   b. Blocks acetylcholine release
   c. Binds GABA-A receptors

d. Binds α-2 receptors.

2. What are the indications for BoNT administration?
   a. Muscle weakness
   b. Muscle hyperactivity
   c. Muscle contractures
   d. Muscle rigidity.
3. When does the maximal effect of BoNT occur?
   a. After 24–72 h
   b. After 3–7 days
   c. Within 10 days to 4 weeks
   d. Within 2 months.
4. What are the most common side effects?
   a. Muscle weakness
   b. Muscle spasm
   c. Rash
   d. Nausea and vomiting.
5. What is a known beneficial effect of casting/taping/splinting?
   a. Decreases muscle synergy
   b. Increases spasticity
   c. Elongates the muscles
   d. Shortens the muscles.

Competency Assessment 3

1. A common side effect of therapeutic nerve block using alcohol or phenol is:
   a. Sedation
   b. Drowsiness
   c. **Dysesthesia**
   d. Diarrhea
2. What is a typical concentration of phenol for spasmolysis?
   a. 1%
   b. 3%
   c. 5%
   d. 7%

Competency Assessment 4

3. In a study comparing ES with anatomic localization, in which muscle was ES found to be superior in correct needle placement?
   a. Gastrocnemius, medial head
   b. Gastrocnemius, lateral head
   c. Soleus
   d. Flexor digitorum longus

References

1. Royal College of Physicians. Spasticity in Adults: Management using Botulinum Toxin. 2nd ed. London: The Royal College of Physicians; 2018. ISBN 978-1-86016-715-7 eISBN 978-1-86016-716-4.
2. Khan F, Amatya B, Bensmail D, Yelnik A. Non-pharmacological interventions for spasticity in adults: An overview of systematic reviews. Ann Phys Rehabil Med 2019;62:265-73.
3. Bavikatte G, Shippen C, Mackarel D, Roberts R, Mackarel S. Spasticity Early & Ongoing Managment Common Patterns • Botulinum Toxin Treatment. United Kingdom: Dr Ganesh Bavikatte, Liverpool; 2017.
4. Gracies JM. Guided Self-Rehabilitation Contract in Spastic Paresis. 1st ed. Springer; 2021. ISBN 978-3-319-29108-6.
5. Chen J, Jin W, Zhang XX, Xu W, Liu XN, Ren CC. Telerehabilitation approaches for stroke patients: Systematic review and meta-analysis of randomized controlled trials. J Stroke Cerebrovasc Dis 2015;24:2660-8.
6. Chen J, Jin W, Dong WS, Jin Y, Qiao FL, Zhou YF, *et al.* Effects of home-based telesupervising rehabilitation on physical function for stroke survivors with hemiplegia: A randomized controlled trial. Am J Phys Med Rehabil 2017;96:152-60.
7. Preissner KS. The effects of serial casting on spasticity: A literature review. Occup Ther Health Care 2002;14:99-106.
8. Tardieu G, Tardieu C. Cerebral palsy. Mechanical evaluation and conservative correction of limb joint contractures. Clin Orthop Relat Res 1987;219:63-9.
9. O'Dwyer N, Neilson P, Nash J. Reduction of spasticity in cerebral palsy using feedback of the tonic stretch reflex: A controlled study. Dev Med Child Neurol 1994;36:770-86.
10. Wilton J. Casting, splinting, and physical and occupational therapy of hand deformity and dysfunction in cerebral palsy. Hand Clin 2003;19:573-84.
11. Law M, Cadman D, Rosenbaum P, Walter S, Russell D, DeMatteo C. Neurodevelopmental therapy and upper-extremity inhibitive casting for children with cerebral palsy. Dev Med Child Neurol 1991;33:379-87.
12. Flett PJ. Rehabilitation of spasticity and related problems in childhood cerebral palsy. J Paediatr Child Health 2003;39:6-14.
13. Marcolino MA, Hauck M, Stein C, Schardong J, Pagnussat AS, Plentz RD. Effects of transcutaneous electrical nerve stimulation alone or as additional therapy on chronic post-stroke spasticity: Systematic review and meta-analysis of randomized controlled trials. Disabil Rehabil 2020;42:623-35.
14. Sohn MK, Cho KH, Kim YJ, Hwang SL. Spasticity and electrophysiologic changes after extracorporeal shock wave therapy on gastrocnemius. Ann Rehabil Med 2011;35:599-604.
15. Manganotti P, Amelio E. Long-term effect of shock wave therapy on upper limb hypertonia in patients affected by stroke. Stroke 2005;36:1967-71.
16. Li TY, Chang CY, Chou YC, Chen LC, Chu HY, Chiang SL, *et al.* Effect of radial shock wave therapy on spasticity of the upper limb in patients with chronic stroke: A prospective, randomized, single blind, controlled trial. Medicine (Baltimore) 2016;95:e3544.
17. Moon SW, Kim JH, Jung MJ, Son S, Lee JH, Shin H, *et al.* The effect of extracorporeal shock wave therapy on lower limb spasticity in subacute stroke patients. Ann Rehabil Med 2013;37:461-70.
18. Santamato A, Notarnicola A, Panza F, Ranieri M, Micello MF, Manganotti P, *et al.* SBOTE study: Extracorporeal shock wave therapy versus electrical stimulation after botulinum toxin type A injection for post-stroke spasticity – A prospective randomized trial. Ultrasound Med Biol 2013;39:283-91.
19. Naro A, Leo A, Russo M, Casella C, Buda A, Crespantini A, *et al.* Breakthroughs in the spasticity management: Are non-pharmacological treatments the future? J Clin Neurosci 2017;39:16-27.
20. Leo A, Naro A, Molonia F, Tomasello P, Saccà I, Bramanti A, *et al.* Spasticity management: The current state of transcranial neuromodulation. PM R 2017;9:1020-9.
21. Mehrholz J, Pohl M, Platz T, Kugler J, Elsner B. Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke. Cochrane Database Syst Rev 2015;2015:CD006876.
22. Allan GM, Finley CR, Ton J, Perry D, Ramji J, Crawford K, *et al.* Systematic review of systematic reviews for medical cannabinoids: Pain, nausea and vomiting, spasticity, and harms. Can Fam Physician 2018;64:e78-94.
23. Wolff V, Jouanjus E. Strokes are possible complications of cannabinoids use. Epilepsy Behav 2017;70:355-63.
24. Cohen K, Weinstein AM. Synthetic and non-synthetic cannabinoid drugs and their adverse effects – A review from public health prospective. Front Public Health 2018;6:162.
25. Aisen ML, Dietz MA, Rossi P, Cedarbaum JM, Kutt H. Clinical and pharmacokinetic aspects of high dose oral baclofen therapy. J Am Paraplegia Soc 1992;15:211-6.
26. Gracies JM, Nance P, Elovic E, McGuire J, Simpson DM. Traditional pharmacological treatments for spasticity. Part II: General and regional treatments. Muscle Nerve Suppl 1997;6:S92-120.
27. Syed YY, McKeage K, Scott LJ. Delta-9-tetrahydrocannabinol/cannabidiol (Sativex®): A review of its use in patients with moderate to severe spasticity due to multiple sclerosis. Drugs 2014;74:563-78.
28. Wissel J. Towards flexible and tailored botulinum neurotoxin dosing regimens for focal dystonia and spasticity – Insights from recent studies. Toxicon 2018;147:100-6.
29. Pirazzini M, Rossetto O, Eleopra R, Montecucco C. Botulinum neurotoxins: Biology, pharmacology, and toxicology. Pharmacol Rev 2017;69:200-35.
30. Dressler D, Mander G, Fink K. Measuring the potency labelling of onabotulinumtoxinA (Botox(®)) and incobotulinumtoxinA (Xeomin

(®)) in an LD50 assay. J Neural Transm (Vienna) 2012;119:13-5.
31. Jost WH, Kohl A, Brinkmann S, Comes G. Efficacy and tolerability of a botulinum toxin type A free of complexing proteins (NT 201) compared with commercially available botulinum toxin type A (BOTOX) in healthy volunteers. J Neural Transm (Vienna) 2005;112:905-13.
32. Park J, Lee MS, Harrison AR. Profile of Xeomin® (incobotulinumtoxinA) for the treatment of blepharospasm. Clin Ophthalmol 2011;5:725-32.
33. Benecke R, Jost WH, Kanovsky P, Ruzicka E, Comes G, Grafe S. A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia. Neurology 2005;64:1949-51.
34. Dressler D. Routine use of Xeomin in patients previously treated with Botox: Long term results. Eur J Neurol 2009;16 Suppl 2:2-5.
35. Ranoux D, Gury C, Fondarai J, Mas JL, Zuber M. Respective potencies of Botox and Dysport: A double blind, randomised, crossover study in cervical dystonia. J Neurol Neurosurg Psychiatry 2002;72:459-62.
36. Rystedt A, Zetterberg L, Burman J, Nyholm D, Johansson A. A comparison of Botox 100 U/mL and Dysport 100 U/mL using dose conversion ratio 1: 3 and 1: 1.7 in the treatment of cervical dystonia: A double-blind, randomized, crossover trial. Clin Neuropharmacol 2015;38:170-6.
37. Mohammadi B, Buhr N, Bigalke H, Krampfl K, Dengler R, Kollewe K. A long-term follow-up of botulinum toxin A in cervical dystonia. Neurol Res 2009;31:463-6.
38. Keren-Capelovitch T, Jarus T, Fattal-Valevski A. Upper extremity function and occupational performance in children with spastic cerebral palsy following lower extremity botulinum toxin injections. J Child Neurol 2010;25:694-700.
39. Do KH, Chun MH, Paik NJ, Park YG, Lee SU, Kim MW, *et al.* Safety and efficacy of letibotulinumtoxinA(BOTULAX®) in treatment of post stroke upper limb spasticity: A randomized, double blind, multi-center, phase III clinical trial. Clin Rehabil 2017;31:1179-88.
40. Carli L, Montecucco C, Rossetto O. Assay of diffusion of different botulinum neurotoxin type a formulations injected in the mouse leg. Muscle Nerve 2009;40:374-80.
41. Yaraskavitch M, Leonard T, Herzog W. Botox produces functional weakness in non-injected muscles adjacent to the target muscle. J Biomech 2008;41:897-902.
42. Eleopra R, Tugnoli V, Caniatti L, De Grandis D. Botulinum toxin treatment in the facial muscles of humans: Evidence of an action in untreated near muscles by peripheral local diffusion. Neurology 1996;46:1158-60.
43. Arezzo JC. NeuroBloc/Myobloc: Unique features and findings. Toxicon 2009;54:690-6.
44. Bakheit AM, Ward CD, McLellan DL. Generalised botulism-like syndrome after intramuscular injections of botulinum toxin type A: A report of two cases. J Neurol Neurosurg Psychiatry 1997;62:198.
45. Bhatia KP, Münchau A, Thompson PD, Houser M, Chauhan VS, Hutchinson M, *et al.* Generalised muscular weakness after botulinum toxin injections for dystonia: A report of three cases. J Neurol Neurosurg Psychiatry 1999;67:90-3.
46. Muller F, Cugy E, Ducerf C, Delleci C, Guehl D, Joseph PA, *et al.* Safety and self-reported efficacy of botulinum toxin for adult spasticity in current clinical practice: A prospective observational study. Clin Rehabil 2012;26:174-9.
47. Kazerooni R, Armstrong EP. Botulinum toxin type A overdoses: Analysis of the FDA adverse event reporting system database. Clin Drug Investig 2018;38:867-72.
48. Hesse S, Krajnik J, Luecke D, Jahnke MT, Gregoric M, Mauritz KH. Ankle muscle activity before and after botulinum toxin therapy for lower limb extensor spasticity in chronic hemiparetic patients. Stroke 1996;27:455-60.
49. Santamato A, Micello MF, Ranieri M, Valeno G, Albano A, Baricich A, *et al.* Employment of higher doses of botulinum toxin type A to reduce spasticity after stroke. J Neurol Sci 2015;350:1-6.
50. Wissel J, Bensmail D, Ferreira JJ, Molteni F, Satkunam L, Moraleda S, *et al.* Safety and efficacy of incobotulinumtoxinA doses up to 800 U in limb spasticity: The TOWER study. Neurology 2017;88:1321-8.
51. Intiso D, Simone V, Bartolo M, Santamato A, Ranieri M, Gatta MT, *et al.* High dosage of botulinum toxin type A in adult subjects with spasticity following acquired central nervous system damage: Where are we at? Toxins (Basel) 2020;12:315.
52. Dressler D, Rothwell JC. Electromyographic quantification of the paralysing effect of botulinum toxin in the sternocleidomastoid muscle. Eur Neurol 2000;43:13-6.
53. Dressler D, Bigalke H. Botulinum toxin type B *de novo* therapy of cervical dystonia: Frequency of antibody induced therapy failure. J Neurol 2005;252:904-7.
54. Naumann M, Boo LM, Ackerman AH, Gallagher CJ. Immunogenicity of botulinum toxins. J Neural Transm (Vienna) 2013;120:275-90.
55. Rosales RL, Kong KH, Goh KJ, Kumthornthip W, Mok VC, Delgado-De Los Santos MM, *et al.* Botulinum toxin injection for hypertonicity of the upper extremity within 12 weeks after stroke: A randomized controlled trial. Neurorehabil Neural Repair 2012;26:812-21.
56. Kinnear BZ, Lannin NA, Cusick A, Harvey LA, Rawicki B. Rehabilitation therapies after botulinum toxin-A injection to manage limb spasticity: A systematic review. Phys Ther 2014;94:1569-81.
57. Mills PB, Finlayson H, Sudol M, O'Connor R. Systematic review of adjunct therapies to improve outcomes following botulinum toxin injection for treatment of limb spasticity. Clin Rehabil 2016;30:537-48.
58. Picelli A, Santamato A, Chemello E, Cinone N, Cisari C, Gandolfi M, *et al.* Adjuvant treatments associated with botulinum toxin injection for managing spasticity: An overview of the literature. Ann Phys Rehabil Med 2019;62:291-6.
59. Carda S, Invernizzi M, Baricich A, Cisari C. Casting, taping or stretching after botulinum toxin type A for spastic equinus foot: A single-blind randomized trial on adult stroke patients. Clin Rehabil 2011;25:1119-27.
60. Wilkenfeld AJ. Review of electrical stimulation, botulinum toxin, and their combination for spastic drop foot. J Rehabil Res Dev 2013;50:315-26.
61. Horn L, Singh G, Dabrowski ER. Chemoneurolysis with phenol and alcohol: A "Dying Art" that merits revival. In: Brashear A, editor. Spasticity. 2nd ed. New York: Demos Medical; 2016.
62. Kolaski K, Ajizian SJ, Passmore L, Pasutharnchat N, Koman LA, Smith BP. Safety profile of multilevel chemical denervation procedures using phenol or botulinum toxin or both in a pediatric population. Am J Phys Med Rehabil 2008;87:556-66.
63. Tilton AH. Injectable neuromuscular blockade in the treatment of spasticity and movement disorders. J Child Neurol 2003;18 Suppl 1:S50-66.
64. Karri J, Mas MF, Francisco GE, Li S. Practice patterns for spasticity management with phenol neurolysis. J Rehabil Med 2017;49:482-8.
65. Kirazli Y, On AY, Kismali B, Aksit R. Comparison of phenol block and botulinus toxin type A in the treatment of spastic foot after stroke: A randomized, double-blind trial. Am J Phys Med Rehabil 1998;77:510-5.
66. Lam K, Wong D, Tam CK, Wah SH, Myint MW, Yu TK, *et al.* Ultrasound and electrical stimulator-guided obturator nerve block with phenol in the treatment of hip adductor spasticity in long-term care patients: A randomized, triple blind, placebo controlled study. J Am Med Dir Assoc 2015;16:238-46.
67. Schnitzler A, Roche N, Denormandie P, Lautridou C, Parratte B, Genet F. Manual needle placement: Accuracy of botulinum toxin A injections. Muscle Nerve 2012;46:531-4.
68. Molloy FM, Shill HA, Kaelin-Lang A, Karp BI. Accuracy of muscle localization without EMG: Implications for treatment of limb dystonia. Neurology 2002;58:805-7.
69. Picelli A, Bonetti P, Fontana C, Barausse M, Dambruoso F, Gajofatto F, *et al.* Accuracy of botulinum toxin type A injection into the gastrocnemius muscle of adults with spastic equinus: Manual needle placement and electrical stimulation guidance compared using ultrasonography. J Rehabil Med 2012;44:450-2.
70. Mayer NH, Whyte J, Wannstedt G, Ellis CA. Comparative impact of 2 botulinum toxin injection techniques for elbow flexor hypertonia. Arch Phys Med Rehabil 2008;89:982-7.
71. Picelli A, Lobba D, Midiri A, Prandi P, Melotti C, Baldessarelli S, *et al.* Botulinum toxin injection into the forearm muscles for wrist and fingers spastic overactivity in adults with chronic stroke: A randomized controlled trial comparing three injection techniques. Clin Rehabil 2014;28:232-42.
72. Picelli A, Roncari L, Baldessarelli S, Berto G, Lobba D, Santamato A, *et al.* Accuracy of botulinum toxin type A injection into the forearm muscles of chronic stroke patients with spastic flexed wrist and clenched fist: Manual needle placement evaluated using ultrasonography. J Rehabil Med 2014;46:1042-5.
73. Henzel MK, Munin MC, Niyonkuru C, Skidmore ER, Weber DJ, Zafonte RD. Comparison of surface and ultrasound localization to identify forearm flexor muscles for botulinum toxin injections. PM R 2010;2:642-6.
74. Bickerton LE, Agur AM, Ashby P. Flexor digitorum superficialis: Locations of individual muscle bellies for botulinum toxin injections. Muscle Nerve 1997;20:1041-3.
75. Delagi EF, Perotto A. Clinical electromyography of the hand. Arch Phys Med Rehabil 1976;57:66-9.