Chapter 11
Botulinum Neurotoxins for Relief of Pain Associated with Spasticity

Abstract Spasticity is a common and disabling complication of stroke, multiple sclerosis, brain and spinal cord injury, and cerebral palsy. Pharmacological treatment, although effective, is confounded by undesirable side effects and short duration of response. Botulinum neurotoxins (BoNTs) have been approved by FDA for treatment of spasticity. The role of BoNT therapy in spasticity-related pain is less established. In this chapter, the literature from double-blind, placebo-controlled studies on this subject is reviewed.

Nine double-blinded, placebo-controlled studies included assessment of pain in the investigation of BoNT efficacy in upper limb spasticity. Four studies that used validated pain scales (visual analog scale, VAS) reported efficacy for abobotulinumtoxinA (aboA) in spasticity-related pain (level A, effective). For lower limb spasticity-related pain, the data is limited to three controlled studies. One study demonstrated efficacy for onaA using a validated pain scale (level B, probably effective) and another for aboA using a scale of 0–5 for assessment of pain. In cerebral palsy (CP), one blinded study reported significant relief of spasticity-related pain after administration of onabotulinumtoxinA (up to 12 units/kg) in children (level B, probably effective, one class I study). A number of open studies have also suggested efficacy for other types of BoNTs in children suffering from CP. Overall, this encouraging literature shows an increasing role for BoNTs in treatment of spasticity-related pain.

Keywords Spasticity • Pain • Botulinum toxin • Botulinum neurotoxin • OnabotulinumtoxinA • AbobotulinumtoxinA • IncobotulinumtoxinA • RimabotulinumtoxinB • Cerebral palsy

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Introduction

Spasticity is a clinical condition caused by damage to the central nervous system (brain or spinal cord) and characterized by a velocity-dependent increase in stretch reflex (muscle tone), in the absence of volitional activity (Lance 1980). Many affected patients also demonstrate pathological reflexes and signs (Babinski reflex, Wartenberg's sign) denoting CNS damage. Spasticity occurs in 38 % of patients with stroke (Watkins et al. 2002), half of the patients with brain injury (Wedekind and Lippert-Grüner 2005), and one third of the patients with spinal cord injury (Noreau et al. 2000). Rizzo et al. (2004) found mild to severe spasticity (19 % mild, 17 % moderate, 13 % severe) in 49 % of 513 patients surveyed from North American registry for multiple sclerosis. In one third of the group, impairment of quality of life could be attributed to spasticity. Lower limb spasticity has been reported in one third of adults after stroke, half to two thirds of patients with multiple sclerosis, and three quarters of children with cerebral palsy (Martin et al. 2014).

Increased tone and stiffness of the muscles in spasticity limits and slows limb movements and, in the lower limbs, also impairs ambulation. Progressive spasticity leads to muscle shortening and contractures with further limitation of movements. Treatment is aimed at reducing muscle tone, preventing complications, and alleviating pain. The incidence of pain in spasticity has not been adequately investigated. In some patients, spasticity-related pain (SRP) is quite severe and more disabling than the spasticity itself.

Pathophysiology of Spasticity and Spasticity-Related Pain (SRP)

The pathophysiology of spasticity has been reviewed recently in a comprehensive two-part article by Gracies (2005a, b). In brief, damage to the central nervous system leads to acute and chronic changes. The acute effects include paresis and short-term immobilization, whereas chronic effects include plastic rearrangements in the CNS as the result of either CNS injury and/or chronic disuse (Fig. 11.1). These changes influence the innervation of the muscles and the reflex arch leading to spasticity, spastic dystonia, and spastic co-contractions. The end result is muscle shortening and contracture caused by chronic spasticity and muscle disuse.

The exact mechanisms through which a state of muscle hyperactivity and spasticity develops after CNS injury are still unclear. As emphasized by Gracies (2005b), extensive sprouting and new synapse formation may play an important role in inducing overactive stretch reflex since the new connections are often hyperexcitable and may act differently from those lost secondary to CNS damage (Gioux and Petit 1993). There is some evidence for both decreased reciprocal I a inhibition (which inhibits alpha motor neurons via a disynaptic interneuron) and decreased I b, nonreciprocal inhibition (which via activity of Golgi tendons limits limb

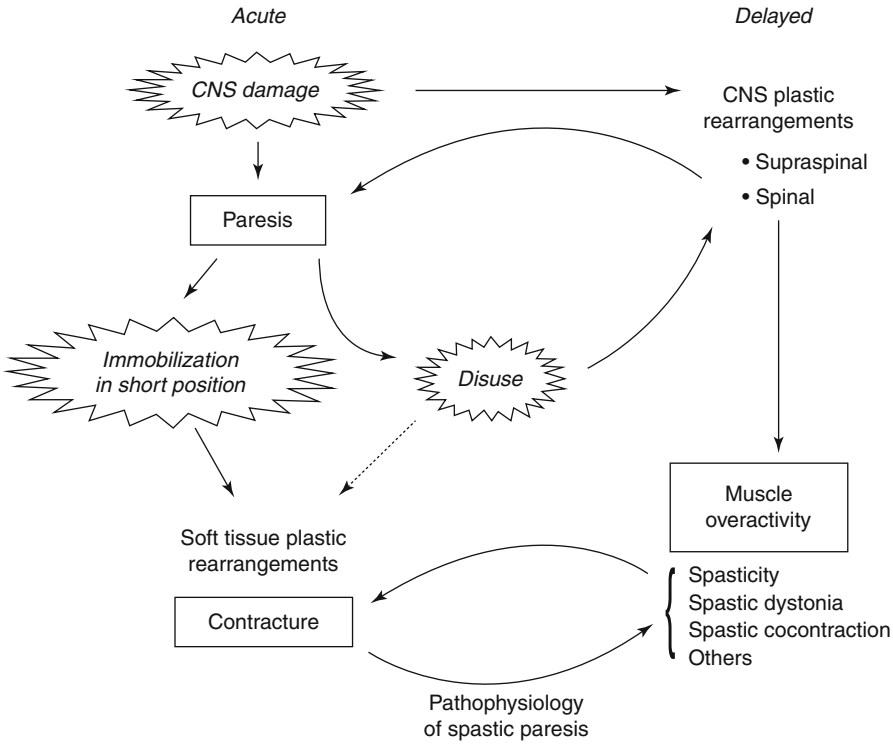

Fig. 11.1 Mechanisms of motor impairment after disruption of the central execution of motor command, paresis, soft tissue contracture, and muscle overactivity (From Gracies 2005 © 2005 Wiley Periodicals Inc, reprinted with permission from John Wiley and Sons)

extension), suggesting contributions from these mechanisms to the increased stretch reflexes in spasticity (Crone et al. 2003). Furthermore, muscle immobility (as seen in spastic paresis) increases the discharge of muscle spindles (Williams 1980) which via the gamma system can lead to increased stretch reflexes and increased muscle tone. Finally, electrophysiological studies of patients with spastic hemiplegia indicate hyperexcitability of small group II afferents (originating from spindle's secondary endings) which in a normal state inhibit motor neurons via spinal interneurons (Marque et al. 2001). The function of these type II afferents is modulated and inhibited by descending rubro- and vestibulospinal pathways that often get damaged in CNS injuries.

On the other hand, Renshaw cell inhibition (RCI) and direct alpha motor neuron hyperexcitability do not seem to play a major role in spasticity. In fact, in human, RCI has been shown to increase after CNS damage and in the presence of spasticity (Katz and Pierrot-Deseilligny 1982).

Spasticity may cause pain through a variety of mechanisms. Some spasticity-related pain (SRP) occurs in the form of muscle spasms caused by increased muscle

tone and enhanced reflex activity. The pain could arise from the affected joints that are limited in movement by the attached stiff, spastic muscles. The frequent pain from spastic muscles and painful joints can also set in motion spinal and supraspinal circuits which cause central sensitization leading to pain chronicity (Chap. 2). In small children, adductor spasticity could lead to hip subluxation and pain.

Treatment of Spasticity

Treatment of spasticity is heavily weighed on pharmacological agents which can cause muscle relaxation. The commonly used drugs for treatment of spasticity include GABAergic agents such as baclofen and benzodiazepines. Tizanidine, an alpha adrenergic drug and a potent muscle relaxant, is also widely used. Unfortunately, severe spasticity often requires larger doses of these medications that are beset by emergence of undesirable side effects (sedation, hypotension). Severe and advanced cases of spasticity (especially in the lower limb) may require baclofen pump placement. Although treatment of spasticity may alleviate the associated pain, in most cases, addition of analgesic drugs is required. The commonly used pharmacological agents include tricyclic antidepressants, nonsteroidal anti-inflammatory agents, and, in severe cases, opioid analgesics.

Botulinum Toxin Studies in Spasticity That Have Included Assessment of Pain

This section covers the blinded studies that assessed pain in adults' upper and lower limb spasticity and in spasticity-related pain of children with cerebral palsy.

Upper Limb Spasticity-Related Pain in Adults

A total of nine blinded and controlled studies included pain assessment among the assessed variables evaluated in the investigation and reported in the results. All nine studies found BoNTs (A and B) to be effective against upper limb spasticity (Brown et al. 2014) which led to the FDA approval of onaA for treatment of upper limb spasticity.

Bakheit et al. (2001), in a blinded, controlled study of 59 patients, first reported on evaluation of BoNT efficacy against pain associated with spasticity. The pain was assessed on a 0–3 scale (no pain to severe pain). AbobotulinumtoxinA, 1,000 units, was injected into different arm and forearm muscles. The authors noted no improvement of pain after aboA administration. In 2004, Childers et al. and Brashear et al. also found no pain improvement in their studies of 91 and 15 patients, respectively. The former authors used three different doses of onaA (90, 180, and 360 units),

while the later employed two doses of rimaB (5,000 and 1,000 units). Childers et al. (2004) assessed pain through a 0–4 scale with four being severe pain, whereas the exact method of pain assessment was not defined in Brashear et al.'s study (2004). In agreement with the above studies, another more recent study which assessed the efficacy of aboA (1,000 units) in 55 patients with spasticity also failed to note any significant improvement in pain after administration of the BoNT into the muscles of the upper extremity (Lam et al. 2012). Since the study was conducted in noncommunicative patients, the evaluation of pain was conducted via an observational 0–5 scale (PAINAD).

In contrast to the aforementioned studies, five other blinded studies of BoNTs and spasticity, four using aboA and one rimaB, reported significant improvement of pain after administration of BoNTs into the upper limb muscles. Four of five of these studies used the validated and widely used visual analog scale (VAS).

Suputtitada and Suwanwela (2005), in a study of 50 patients, reported significant improvement of pain after administration of aboA (three doses: 375, 500, and 1,000 units) injected into spastic upper limb muscles. The positive result of this study was supported by another blinded study (Marco et al. 2007) of aboA in spasticity that used 500 units. The assessment tool for pain was VAS in both studies.

Another two blinded studies of BoNT treatment in spasticity that assessed pain via VAS also reported significant pain relief. Shaw et al. (2011) enrolled 333 patients with spasticity in a prospective, placebo-controlled, blinded study. Patients received either placebo, 100, or 200 units of aboA in the spastic upper limb. Reinjections were performed at 3, 6, and 9 months. A significant improvement of pain was noted at 12 months but not at 1 and 3 months. In another blinded study of 163 patients (Rosales et al. 2012), administration of 500 units of aboA into the arm and forearm muscles caused significant pain relief at 4 and 24 months. Marciniak et al. (2012) assessed pain through the short-form McGill Pain Questionnaire in 37 patients with post-stroke shoulder spasticity who participated in a double-blind trial investigating the efficacy of onaA (140–200 units) in spasticity. At 4 weeks, pain was significantly reduced ($P<0.05$) compared to baseline, but the placebo group also demonstrated the same degree of pain reduction.

A recent double-blind study (Gracies et al. 2014) that used rimaB toxin (5,000 and 10,000 units) in elbow flexors also demonstrated significant reduction of pain at 1 month following toxin injection ($P=0.017$). The main features of the nine double-blinded BoNT spasticity studies that have reported on the results of pain assessment are presented in Table 11.1.

Comment

At first glance, the results of BoNT treatment in spasticity-related pain from the nine blinded studies mentioned above may appear controversial or contradictory (four against and five in favor). A more careful evaluation of these studies, however, provides useful explanations for the apparent contradictory results. All four studies

Table 11.1 Blinded, botulinum toxin treatment trials of upper limb spasticity which included assessment of pain

Study	# of pts	Class	Toxin	Dose (U)	Pain scale	Result compared to baseline	Comment
Shaw et al. (2011)	333	I	AboA	100/200	Mean VAS	No significant change at 1 and 3 month. At 12 months, $P=0.002$	Delayed pain relief
Suputtitada and Suwanwela (2005)	50	I	AboA	375/500/1,000	Pain scale?	Improved	
Marco et al. (2007)	31	I	AboA	500	Mean VAS	Pain reduction noted on weeks 1, 2, 3, 4, 5, 6 months ($P=0.001$)	
Rosales et al. (2012)	163	I	AboA	500	Mean VAS	Significant pain reduction weeks 4 and 24	
Childers et al. (2004)	91	I	OnaA	90/180	5-point scale	No significant change	Unvalidated scale?
				360			Low baseline pain
Brashear et al. (2004)	15	I	RimaB	5,000 and 10,000	Pain scale?	No significant change	
Bakheit et al. (2001)	59	I	AboA	1,000	0–3 pain scale	No significant change	Unvalidated scale?
Lam et al. (2012)	55	I	AboA	1,000	Observational scale 0–5	No significant change	Unvalidated scale?

that used an established and validated pain assessment tool (in this case VAS) reported efficacy against pain. Using the assessment criteria of the American Academy of Neurology (Appendices 3.1 and 3.2), the level of evidence for efficacy for aboA in spasticity-related pain of the upper limb (using VAS for pain assessment) is A (established efficacy based on two or more class I studies). The delayed efficacy (at 12 months, probably after third injection) in the study of Shaw et al. (2011) is most probably related to the small dose of aboA used by the investigators (100 and 200 units versus 500 and 1,000 units used by others). Such cumulative, late effect after repeat injections has been reported in other pain indications after BoNT treatment especially with onaA administration in chronic migraine (Aurora et al. 2014). The efficacy of aboA in relieving spasticity-related pain is supported by a recent large prospective, open-label European study (Jost et al. 2014) of 408 patients in which 58.9 % of the patients reported pain relief. Evaluation of the efficacy of the other forms of botulinum neurotoxin in spasticity-related pain deserves further investigation via placebo-controlled studies.

Case Report

A 65-year-old gentleman had suffered an acute cerebral infarct and a left hemiparesis 3 years earlier. The left-sided weakness gradually improved with physical therapy and regular exercise. He visited Yale Botulinum Toxin Treatment Clinic for evaluation and management of spasm and pain in the left pectoralis major and left trapezius muscle. The pain was constant for the past 6 months but also occurred in the form of intermittent spasms and interfered with his sleep.

On examination, the left shoulder was elevated, and the left trapezius muscle demonstrated increased tone. The left pectoralis major muscle was also spastic which, at rest, caused over-adduction of the left arm. Under electromyographic guidance, 120 units of onabotulinumtoxinA was injected into the trapezius and pectoralis muscles (each muscle received 20 units in three sites for a total of 60 units) (Figs. 11.2 and 11.3). After 1 week, the patient reported cessation of spasms and marked improvement of daily discomfort. Repeat injections every 3 months remained effective 4 years postinjection of therapy and are ongoing.

Lower Limb Spasticity-Related Pain of Adults

Three double-blind, placebo-controlled studies have reported on the effects of BoNTs on lower limb spasticity-related pain.

Hyman et al. (2000) studied 74 patients with lower limb spasticity stratified into four groups: placebo group and three groups receiving aboA with doses of 500, 1,000, and 1,500 units, respectively. The frequency of muscle spasms was assessed among other assessments. The authors reported that the frequency of muscle spasms improved in all groups, but the difference between the groups was not significant.

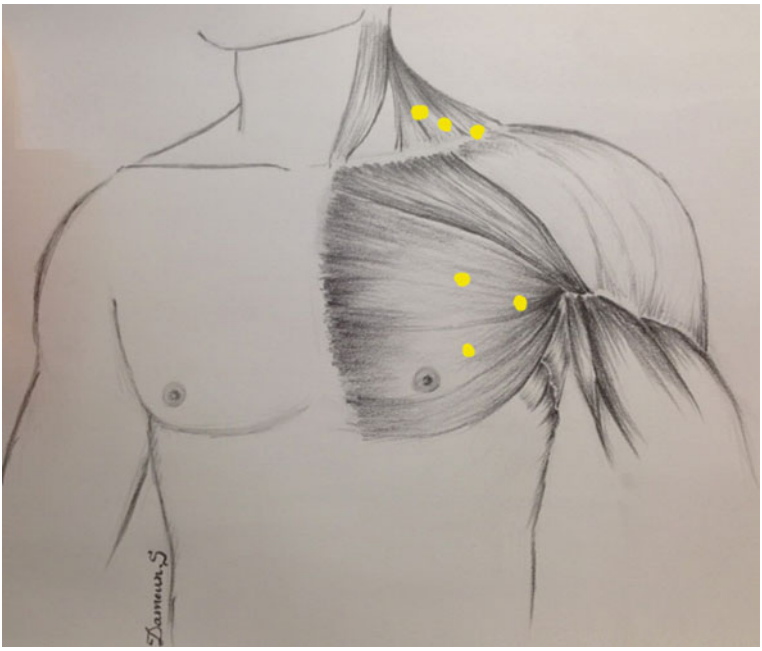

Fig. 11.2 Location of botulinum toxin injections in case 11-1, with left trapezius and left pectoralis major spasticity and pain after stroke. In each muscle, 20 units of onaA is injected in three sites (60 units/muscle) (Created by Damoun Safarpour; published with kind permission of © Bahman Jabbari 2014. All Rights Reserved)

Another group of investigators (Pittock et al. 2003) used the same study design assessing the efficacy of aboA in calf spasticity after stroke. The study encompassed a much larger group of patients (234 from 19 centers), stratified into four groups of placebo and aboA toxin (500, 1,000, and 1,500 units). Injections were made at 4 points into the gastrocnemius muscle. The authors used a 0–3 scale for severity of pain. No pain relief was seen in the placebo group. All three aboA groups reported significant pain relief which was more notable at 8 weeks with 1,000 units ($P=0.0019$) and 1,500 units ($P=0.0066$) but also at 4 weeks ($P=0.0044$ and $P=0.0040$, respectively) and 12 weeks ($P=0.0128$ and $P=0.0488$, respectively). A lower level of pain relief was noted at 8 weeks in the group receiving 500 units ($P=0.0222$).

Dunne et al. (2012) investigated the efficacy of onabotulinumtoxinA in 85 patients (multicenter study) with painful plantar flexor/inverter spasticity after stroke. The frequency of painful spasms was assessed before and after treatment. Three study groups were designed to receive saline, 100, and 200 units of onabotulinumtoxinA. The onabotulinumtoxinA-injected subjects showed significant reduction of spasm frequency (22/54 versus 4/29, $P=0.01$), pain reduction (8/54 versus 1/29, $P=0.02$), and active dorsiflexion (8/54 versus 1/29 $P=0.03$).

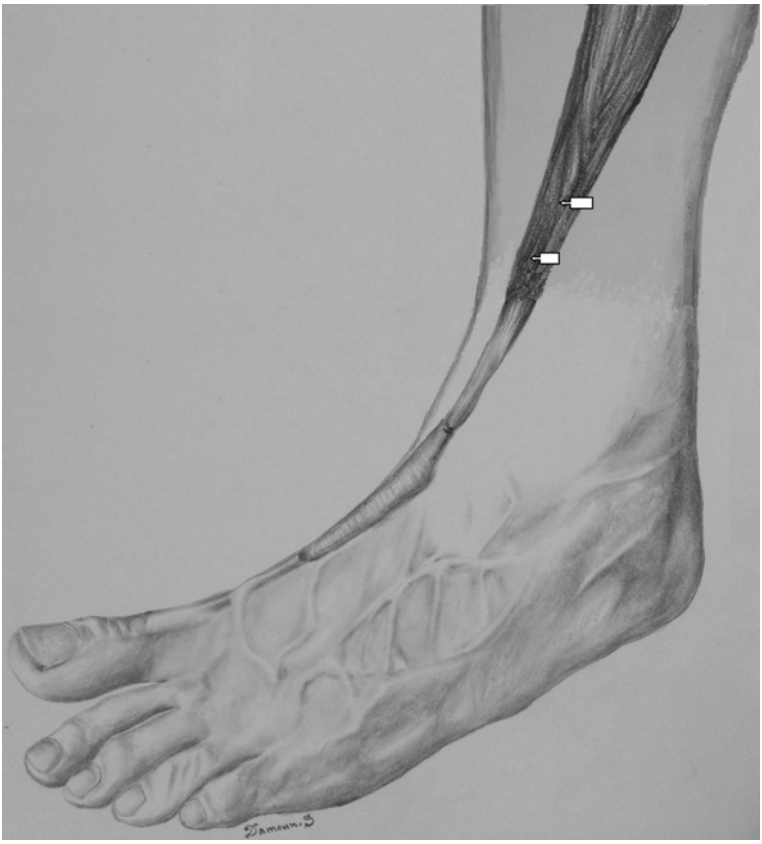

Fig. 11.3 Location of botulinum toxin injection into the extensor hallucis muscle of a patient with multiple sclerosis for relief of spastic, extended, painful big toe. A total of 100 units was injected into two sites (50 units/site) (Created by Damoun Safarpour; published with kind permission of © Bahman Jabbari 2014. All Rights Reserved)

Recently, in a prospective, open-label study (Santamato et al. 2013) of 71 patients with lower limb spasticity using incobotulinumtoxinA (N201), the authors reported significant reduction of spasm frequency at 30 and 90 days. The total dose administered to each patient per session was 180 units. The notable features of BoNT studies in spasticity-related pain of the lower limbs are shown in Table 11.2.

Comment

Information regarding the effects of BoNT therapy on lower extremity spasticity-related pain in adults is limited. Level B efficacy (probably effective) can be ascribed to both aboA (one class I study, Pittock et al. 2003) and rimaA (one class

Table 11.2 Blinded, botulinum toxin treatment trials in lower limb spasticity which included assessment of pain

Study	# of pts	Class	Toxin	Dose (U)	Pain scale	Result compared to baseline	Comment
Hyman et al. (2000)	74	I	AboA	500/1,000, 1,500	Frequency of spasms	Frequency improved in all groups. No difference between groups	No values provided large placebo effect
Pittock et al. (2003)	233	I	AboA	500/1,000	0–3 scale	Significant improvement at 4, 8, 12 weeks ($P<0.005$) in 1,000 and 1,500 unit group—in 500 unit group week 4 ($P<0.005$)	
Dunne et al. (2012)	85	I	OnaA	100/200	VAS and spasm frequency	VAS: improved ($P=0.02$), spasm frequency improved ($P=0.01$)	

I study, Dunne et al. 2012) based on the subcommittee guidelines of AAN (Appendices 3.1 and 3.2). The study of Hyman et al. (2000) is hard to interpret due to the paucity of information. The fact that both the placebo and toxin improved pain significantly may imply a large placebo effect and does not necessarily negate the efficacy of the toxin.

Effects of BoNT Treatment on Spasticity-Related Pain in Children with Cerebral Palsy

Performance of double-blind studies for assessing the efficacy of BoNTs on spasticity or spasticity-related pain in children with cerebral palsy is difficult due to procedural and ethical issues. The issue of treatment of pain with BoNTs in children with CP pertains both to treatment of existing spasticity-related pain and to preventing spasticity-related complications which can cause future pain and problems (e.g., hip subluxation in small children).

One double-blind, placebo-controlled study and a number of open-label (prospective and retrospective) studies have evaluated the effect of BoNT treatment on spasticity-related pain of children with cerebral palsy. These studies uniformly report improvement of spasticity-related pain in children with cerebral palsy. The double-blind study is described in some detail below followed by a brief description of the two open studies.

Copeland et al. (2014) studied 41 nonambulatory children with advanced spasticity and cerebral palsy. The study was prospective and double blind. The mean age of the children was 7.1 years. Twenty-three received BoNT-A and 18 received a sham procedure. The efficacy of injections was assessed during a 12-month follow-up period by physicians using a Modified Ashworth Scale, joint range of motion, Physician Rating Scale, Gillette Functional Assessment Questionnaire, and Gross Motor Function Measure-66 and by patients/parents using visual analog scale and the Pediatric Pain Profile (PPP). OnabotulinumtoxinA was injected into spastic muscles using a maximum dose of 12 units/kg or a total dose of 400 units per session. Following administration of onaA, in addition to improvement of the aforementioned parameters, the children who received BoNT injections (and parents) reported significant reduction of pain compared to baseline at 4 and 16 weeks (P values <0.05 and <0.01, respectively). In the sham procedure group, no significant response was observed.

In a study of 26 children with CP, spasticity, and hip pain (Lundy et al. 2009), investigators injected either onaA (nine children) or aboA (17 children) into the adductor magnus, hamstring, and iliopsoas muscles. The dose per session was up to 12 units/kg for onaA and up to 30 units/kg for aboA. The pain was measured by Pediatric Pain Profile. Injection of both neurotoxins resulted in marked reduction of pain at 3 months ($P=0.001$).

A multicenter, prospective, observational study from France (Chaleat-Valayer et al. 2011) reported on the treatment of 286 children suffering from CP with botulinum toxin A, followed for 12 months. Administration of botulinum toxin A improved range of motion, movement capacity, gait, and spasticity-related pain.

Rivard et al. (2009) asked the parents of 34 children with CP (mean age 9) and spasticity-related pain about the intensity and frequency of pain after BoNT-A injection into spastic muscle. The parents reported cessation of pain at week 4 in 62 % of the children.

In very young children, cerebral palsy with bilateral proximal lower limb spasticity often causes hip dislocation resulting in significant pain, impaired ambulation, and disability. In a study of 98 children, Pascale-Leone from La Paz Hospital in Madrid (2003) found continuous worsening of lateral hip migration in 86 % and full subluxation in 11.4 %. Administration of BoNT into the hip adductor and iliopsoas muscles stopped the progression in 74 % of the children via reduced spasticity and reverted the condition in another 14 %. The author advocates early and aggressive treatment, every 3–4 months, to prevent this complication.

In collaboration with our pediatric neurologist, Marc Difazio M.D, we treated and followed over 200 children with cerebral palsy with onabotulinumtoxinA at Walter Reed Army Medical Center, Washington DC. Some of the children were followed up to 8 years. The maximum dose used per session was 12 units/kg. Injections (upper or lower limb) were very effective in reducing spasticity, improving quality of life (sleep, hygiene, mood, irritability), and reducing pain. In general, parents were very satisfied with the results. No serious side effects were noted during the 8-year follow-up. My continued experience with treatment of child spasticity with onabotulinumtoxinA at Yale (past 10 years) agrees with my practice in the Washington area. The results are very much appreciated by the parents.

The Mechanism of Action of BoNTs in Spasticity-Related Pain (SRP)

The mode of action of BoNTs in SRP most probably involves both muscular and neural mechanisms. On the muscular side, BoNTs block the release of acetylcholine from presynaptic vesicles causing muscle relaxation that in turn can reduce the frequency of painful spasms. Furthermore, relaxation of muscles leads to better joint motility and prevents secondary pain and discomfort related to awkward joint-muscle interactions. In children, focused relaxation of hip adductors can prevent subluxation and related discomfort. On the neural side, some of the pain in advanced spasticity and contracture may originate from peripheral nerve fibers in the affected contracted tissue. Numerous animal studies have shown that BoNTs inhibit the release of pain mediators (glutamate, substance P, and calcitonin gene-related peptide) from peripheral nerve endings and dorsal root ganglia (Chap. 2).

Also, it is now increasingly recognized that peripheral injection of BoNTs (intramuscular or subcutaneous) has a direct central effect via retrograde transport and transcytosis (Mazzocchio and Caleo 2014). In support of the central effect of the toxin, Bach-Rojecky et al. (2010) have shown bilateral improvement of leg hyperalgesia after unilateral injection of onabotulinumtoxinA into the affected area on one side. Furthermore, following injection of the toxin into the rat's eye, truncated SNAP25 was detected in the midbrain tectum terminals despite the Wallerian degeneration of the axon that transports the toxin (Restani et al. 2012).

Such central effects can invariably impact the function of spinal circuits, interneurons, and spinal sensory neurons, all of which play an important role in spasticity and spasticity-related pain.

Conclusion

Blinded and placebo-controlled studies of adult spasticity have illustrated the efficacy of abobotulinumtoxinA in the management of upper limb spasticity-related pain. In lower limb spasticity-related pain, however, data is still limited though it strongly suggests efficacy. Studies in children with cerebral palsy suggest efficacy of different types of BoNTs in reducing spasticity-related pain. BoNT injection into spastic hip adductor muscles of children with CP may be helpful in preventing the painful and serious complication of hip subluxation.

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