Chapter 6

Use of Botulinum Toxin A in Cerebral Palsy

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Additional information is available at the end of the chapter

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Abstract

Botulinum toxin A (BTX-A) is widely used worldwide to overcome the significant problem in spastic cerebral palsy (CP). In the past three decades, botulinum toxin serotype A (BTX-A) has been introduced as a selective treatment option for spasticity in children with cerebral palsy. BTX-A is an acetylcholine-blocking agent that causes presynaptic neuromuscular blocking when injected into the muscle. Its action of decreasing or normalization of tone prevent the development of contractures and deformities and avoid or postponed surgical intervention particularly when combined with other treatment modalities such as physiotherapy, casting, orthosis, etc. Equinus deformity, scissoring and crouch gait in the lower limbs, and different spastic deformities like pronation of forearm, elbow flexion, wrist flexion, fisting, or abnormal dystonic posture of upper limb deformities were the main indications wherein botulinum toxin injection is needed in spastic cerebral palsy; moreover, its benefit of relieving pain that are associated with muscular hypertonia and palpation of the muscle, particularly the large one, remains the cornerstone for injection of BTX in CP patient for most experts worldwide, but it needs a well of knowledge in anatomy and its landmark. Invasive procedure like electromyography (EMG) is more difficult to be applied successfully in children than in adults. Spasticity is considered a positive phase of muscle function. Therefore, when relaxing the muscle, the patient's condition might get worse functionally in some instance. So, the first question clinician put in his account before injecting BTX is whether hypertonia is impeding or improving function; therefore, injection is tailored individually by an expert physician. Generally, the adverse side effects of BTX-A are seldom to occur providing that the physician strictly adheres to the dose ranges and reinjection period. The interinjection period must be at least 12 weeks to avoid antibodies ands. So far, BTX-A is considered to be safe to some extent if used professionally; however, long-term adverse effect particularly with multilevel therapy are still not clear.

Keywords: cerebral palsy, botulinum toxin, spasticity, muscle function, children

1. Introduction

Cerebral palsy (CP) is a nonprogressive encephalopathy that primarily affects motor system; in consequence, there is a defect in motor milestone development with a variable degree of severity and locomotor deformities. Therefore, CP is a complex entity with known and unknown causes [1].

Cerebral palsy (CP) is the most frequent cause of spasticity in children [2]. In the last 25 years, injecting botulinum toxin type A (BTX-A) has been proven as an effective medicine strategy to decrease hypertonia in CP child. Now used in most countries of five continents, it is a green light after 2 years of age adopted by most expertise; however, there is big difference in licensing from one country to another. Therefore, most of BTX-A use is labeled according to its trademark. Nowadays, BTX-A has a major role of the multidisciplinary treatment in spastic CP, in addition to physiotherapy, occupational therapy, speech therapy, casting, ankle-foot orthoses (AFO), and knee-ankle-foot orthosis (KAFO) surgical application of intrathecal baclofen; selective dorsal rhizotomy (SDR); and different orthopedic interventions, with varying simple to complex intervention to achieve optimal reconstructive [3].

Within the current clinical management of CP in children, the use of BTX-A is recommended to improve function and to support motor development [4]. Botulinum toxin injection has an additional role on the decrease of pain associated with focal spasticity [5]. Actually, in muscular hypertonia, sever muscle contraction produces compromising vessel resulting in ischemia, ultimately agonizing nociceptive pain (ischemic muscular pain). Nevertheless, decrease of spasm by BTX injection improved blood flow, the ischemia markedly decreased, and pain subsided by muscular relaxation effect of BTX [6].

BTX had been discovered at the beginning of the nineteenth century as a poison. This poison is a protein, which is a product of *Clostridium botulinum* bacterium, a Gram-positive anaerobe. Meat is considered the primary source of this bacterium, from the name "botulus" which mean sausage, though it is present in different food types. The German physician Justinus Kerner in 1818 first wrote about poison that food-borne diseases who was described confidently in the middle-aged patient. The features of botulism have been known since ancient times around the time of Christ [7]. He then published a monograph on poisoning in 1820 in which he described the features, made many original observations, and commented on the possible causation, diagnosis, and treatment [8]. He concluded that a toxin produced by an infective agent was responsible for the features of paralysis of skeletal and smooth muscles. He published a second monograph in 1822, in which he laid out his hypotheses on BTX and described clinical evaluation of the problem through case histories of his patients and through post-mortem examination of patients with botulism [9].

1.1. Physiology of neuromuscular transmission

When we take neuromuscular junction (NMJ) in focus, it consists of the terminal branch of the motor neuron and the muscle fiber that innervates and synaptic cleft between. Acetylcholine is synthesized and stored in the synaptic vesicles that are released into the synaptic cleft by fusion with the presynaptic membrane, through the process called exocytosis. The process of

exocytosis is a result of a nerve action potential arriving at the terminal membrane causing an influx of calcium ions through voltage-dependent channel and binding to the receptors on the postsynaptic neuron, causing a change in the electrical properties of that membrane, which finally results in the contraction of the muscle fiber. Calcium regulated the process of exocytosis which is considered a complicated process that involves the actions of proteins located on the vesicles in the cytosol and on the presynaptic membrane. The protein known as synapsin I binds to the synaptic vesicle to the cytoskeleton. Calcium-dependent process known as synapsin I phosphorylation leads to the release of the vesicle from the cytoskeleton and then is transported into the active zone, where it binds to the presynaptic membrane [10]. The synaptic vesicle contains other important proteins; synaptobrevin and syntaxin on the presynaptic membrane act as shelter that pulls the membranes together. On the other hand, synaptosome-associated protein 25, which is attached to the presynaptic membrane, binds to two molecules of syntaxin, which forms a complex [11]. Synaptobrevin binds to this complex and displaces one of the syntaxin molecules from the complex, which brings the synaptic vesicle and the presynaptic membrane into the proximity that is necessary for fusion and exocytosis to take place [10].

From the above, we conclude that exocytosis is considered the primary mechanism for the release of acetylcholine, and this process is complicated and not fully investigated; however, it involved a lot of specific proteins. Therefore, any intervention with these proteins impaired acetylcholine release by exocytosis which results in presynaptic blocking, and this is what happens with BTX.

2. Mechanism of action of botulinum toxin

Botulinum neurotoxin is indeed a remarkable protein produced by *Clostridium botulinum* [12]; there are at least seven serotypes of neurotoxin discovered till now: botulinum toxin A (BTX-A), botulinum toxin B (BTX-B), botulinum toxin C (BTX-C), botulinum toxin D (BTX-D), botulinum toxin E (BTX-E), botulinum toxin F (BTX-F), and botulinum toxin G (BTX-G), only first two are medically used. Neurotoxins share with same target to inhibit presynaptic acetylcholine release to synaptic cleft, but they are different in targeting protein, their duration of effect, and their potency [13, 14]. BTX-A displays their effect in relaxing the muscle proportionally related to doses [15, 16].

The effect of BTX lasts for about 12–16 weeks; however, within 4 weeks soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex of protein has its turnover. Exocytosis resumes and new axonal sprouting is at the end plate to reestablish conduction [17].

2.1. Pharmacological aspects of botulinum toxin therapy

Botulinum toxin drugs currently available (BTX drugs) are Botox (Allergan Inc., Irvine, CA, USA), Dysport® (Ipsen Ltd., Slough, Berkshire, UK), NeuroBloc/Myobloc (Solstice Neurosciences Inc., Malvern, PA, USA), and Xeomin (Merz Pharmaceuticals, Frankfurt/M, Germany). From 1989 to 1992, Botox's trade name was Oculinum®. In the USA and in some

other countries, NeuroBloc is distributed as Myobloc. Additional BTX drugs include Hengli (Lanzhou Institute of Biological Products, Lanzhou, Gansu Province, China), which is based upon BTX type A and which is distributed in some other Asian and South American markets as CBTX-A or Prosigne®, and Neuronox® (Medy-Tox, Ochang-eup, South Korea), which is sold in South Korea and in some other Asian countries. New BTX drugs are underdevelopment at Tokushima University, Tokushima City, Japan, and at the Mentor Corporation, Santa Barbara, CA, USA. Botox was the first BTX drug to be registered in 1989, while Dysport was registered in 1991, Hengli in 1993, NeuroBloc/Myobloc in 2000, and Xeomin in 2005.

Most of the currently available BTX drugs are shown in **Figure 1**. All BTX-A drugs are powders which need to be reconstituted with 0.9% NaCl/H2O prior to application. Only NeuroBloc/Myobloc is a ready-to-use solution. For all BTX drugs, special storage temperatures are required. Xeomin is the only drug which can be stored at room temperature. The shelf lives of all BTX drugs are similar. The long shelf life of Xeomin is remarkable, since it was originally believed that the lack of complexing proteins would destabilize its BTX. Since NeuroBloc/Myobloc is stabilized by a reduced pH value, about half of the patients receiving NeuroBloc/Myobloc report intensified application pain.

2.2. Patient selection

The selection of CP patient who is a candidate for BTX-A application is based on clinical evaluation of spasticity, power, posture, gait, and other motions, rang of motion, and joint assessment whether dynamic or limited by contracture. Nevertheless, an accurate choice of the CP child for BTX-A might be difficult and need more complex assessment because of the dynamic character of spastic CP and must include motion [18].

Many studies adopted the relation between gait analysis assessment and clinical assessment; they found that both are complementary to each other in providing important information for planning the strategy of CP management. Therefore, observation of movement specially if combined with gait analysis data provides important information in selection of target muscles [19]. Assessment of motion at each joint with identification of spastic muscle that needs to be injected by BTX could be achieved by motion/gait analysis [20].

From these assessments, we conclude that motion analysis in the different anatomical posture for children while walking, crawling, sitting, rolling by physician, and videotaping is considered important in optimizing the benefits of BTX injection.

In nonambulatory CP child with Gross Motor Function Classification System [GMFCS] IV and V, x-rays are indicated in their regular follow-up, to rule out and develop hip dysplasia and scoliosis/kyphosis.

2.3. The use of botulinum toxin in cerebral palsy

There are many causes of cerebral palsy (CP) that make normal development of the limb without deformity and difficulty, but spasticity remains the most important cause as spastic muscle interferes with the neighboring bone and soft tissue growth, resulting in discrepancy

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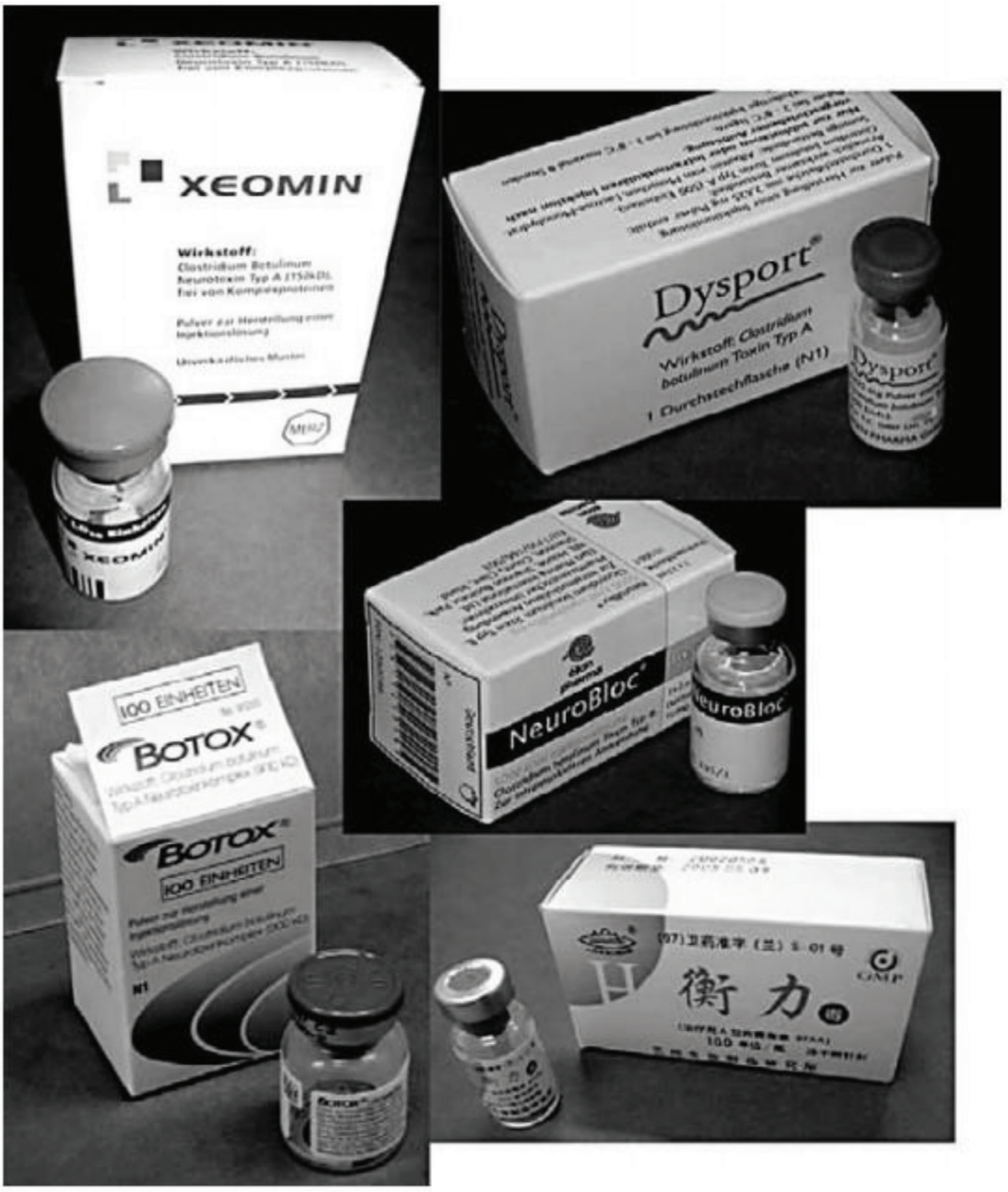

Figure 1. Some of the commercially available botulinum toxin drugs.

in growth between spastic muscle and other structures, with time of growing child dysmorphism and contracture of limb occurring with consequent loss of normal function with shortening of both the muscle and the limb if the tone is constantly remained hypertonic [21]. Such evidence of impairment of growth and deformity is also noted in animals with spasticity, for instance, spastic mouse [22]. Fortunately, stretching of the relaxed muscle may ensure no deformity and contracture with normal growth [23]. According to this hypothesis, it has been supposed that great benefit could be gotten from BTX from its action of relaxing the muscle in spastic CP, and this premise has been tested in mice with significant result regarding restoring the muscle length to normal [24].

Additional benefit from BTX injection to the hypertonic muscle enhances the reciprocal antagonist muscle to become stronger, with subsequent decrement of bone deformity as a result of decrease in discrepancy of impaired growth of spastic muscle and neighboring structure. Indeed, there is clear evidence of delay or decrease of the need for surgical intervention with injection of BTX specially if combined with other models of management such as physiotherapy, casting, and orthotics. However, to achieve optimum goal of BTX injection, many factors are required, but the appropriate selection of the patient is the most important domain for the success of BTX injection. The patient should not have fixed contracture, and spastic patient with dynamic joint is considered typical for injection, whereas the patient with dyskinesia has mild to moderate effect. Athetoid types of CP usually do not get benefit [25].

Anyhow, management target is to progress normal sequence of milestone and attain the next motor development. The goal of treatment in ambulatory patient is to improve and optimize ambulation and walking [16]. **Table 1** shows special indication.

2.4. Muscles of upper extremities

Many muscles in the upper limb are targeted by BTX injection. Again, selection of spastic muscle depends upon the patient's state. Therefore, evaluation and assessment of the patient of proposed benefit functionally avoiding bone deformity are individualized according to the patient [26].

In the upper limb, the injection depends upon the spasticity pattern. For instance, spastic flexion of the elbow usually is in the brachioradialis muscle with or without biceps brachii muscle. For spastic forearm pronation injection will be in the pronator teres, while for spastic wrist flexion, the muscles involved with injections are flexor carpi radialis and flexor carpi ulnaris. Moreover, spastic flexion of the finger needs injection to flexor digitorum profundus and superficialis, while adductor pollicis for the thumb commonly injected if the spastic thumb in the hand posture. The most common muscles injected for spastic shoulder deformity are triceps brachii, pectoralis muscles, teres major, and deltoid [27].

Of note there is some time clinical modification which is individualized according to the patient. For instance, in elbow flexion maximum dose to brachioradialis muscle and minimum or no injection of biceps brachii muscle to maintain function of arm in bearing things and in wrist spastic flexion maximum dose to flexor carpi ulnaris muscle if ulnar deviation of hand present. The injection of BTX should be done by an expert with well surface anatomical knowledge and choice large bulk of muscle with injection to near neural plate which is expected near to the mid-belly. **Table 2** shows BTX injection of upper extremities.

2.5. Muscles of lower extremities

The lower limb muscle injection is considered the most important in spastic cerebral palsy via its benefit to decrease deformity and improve gait. The gastrocsoleus complex is considered the most common site of injection in dynamic toe-walking spastic CP patient, combined with injection to tibialis posterior for dynamic equinovarus deformity. These injections are considered typical in spastic diplegic CP and spastic hemiplegic CP. Other important lower

Indication/clinical pattern	Goals	Muscles involved	Dose (U/kg) of Botox®	Number of sites
Externally rotated shoulder	Ease shoulder adduction	Infraspinatus	1–2	1–2
	Improving gait	Teres minor	1	1
	Enhance dressing	Long head of triceps	2–3	2–3
	Ease reaching	Latissimus dorsi	1–4	2
Adducted/internally rotated shoulder	Ease shoulder abduction	Pectoralis major	2	2–3
	Improving gait	Subscapularis	1	1–2
	Enhance dressing	(Teres major)	1	1
		(Latissimus dorsi)	1–4	2
Flexed elbow	Allow extension of the elbow	Biceps brachii	2–3	2–4
	Enhance reaching	Brachialis	2	1–2
		Brachioradialis	1–2	1
Pronated forearm	Allow supination	Pronator teres	1	1
	Improve dexterity	Pronator quadratus	1	1
Flexed wrist	Ease wrist extension	Flexor carpi radialis	1–2	1
	Ease wearing orthoses	Flexor carpi ulnaris	1–2	1
Clenched fist/hand	Improve hand opening	Interosseous muscles	0.5–1	1
	Improve wearing orthosis	Lumbricalis muscles	0.5–1	1
	Ease cleaning of the palm	Flexor digitorum superficialis	1–2	1–4
		Flexor digitorum profundus	1–2	1–4
		Flexor pollicis longus	1–2	1–2
Thumb in the palm	Enhance thumb abduction	Adductor pollicis brevis	0.5–1	1
	Help pinch and opposing	Flexor pollicis brevis	0.5–1	1
	Improve wearing orthosis	Flexor pollicis longus	0.5–1	1
	Ease hand opening	Interosseous dorsalis I	0.5–1	1
Flexed hip	Improving gait	Iliacus/psoas	2–4	1–2
Crouch gait	Enhance hip extension	Rectus femoris	1–3	2
Stiff knee	Improving swing phase by easing knee flexion	Rectus femoris	1–3	2
Scissoring gait, adducted thighs	Improve abduction and decrease scissoring gait	Adductor longus	1–4	1–2
	Better perineal hygiene	Adductor brevis	1–4	1–2
	Ease wearing abductor braces	Adductor magnus	1–4	1–2
	Improving sitting	Gracilis	1–2	1–2

Indication/clinical pattern	Goals	Muscles involved	Dose (U/kg) of Botox^{R}	Number of sites
Flexed knee	Improving balance and gait	Semitendinosus	1–3	1–2
Crouch gait	Enhance heel strike in stance	Semimembranosus	1–3	1–2
	Ease sitting	Biceps femoris	1–3	1–2
		Gastrocnemius mediale/ laterale	3–6	1–4
Striatal toe	Ease footwear	Extensor hallucis longus	1–2	1
Toe clawing	Improve balance and gait	Flexor digitorum longus/ brevis	1–2	1
	Prevent toe-turn	Flexor hallucis longus	1–2	1
Equinovarus foot	Improve plantar flexion	Gastrocnemius mediale	1–3	1–2
	Enhance heel strike in stance	Gastrocnemius laterale	1–3	1–2
	Improving balance and gait	Soleus	1–3	1–2
	Ease wearing orthosis	Tibialis posterior	1–2	1–2

Table 1. Indication, dose, target muscle, and number of injection [16, 30, 31].

Muscles injected	Dose range (IU/kg of bw)	Number of sites
Adductor pollicis	0.5–1	1
Flexor pollicis longus	0.5–1	1
Flexor digitorum profundus	2	1–2
Flexor digitorum superficialis	2	1–2
Flexor carpi ulnaris	2	1
Flexor carpi radialis	2	1
Pronator teres	1	1
Biceps	2	2–3

Table 2. Muscle injected, dose, and number of injection of upper extremities [30].

limb BTX injections are semitendinosus and semimembranosus of hamstring muscles in order to decrease hypertonia of these muscles in dynamic knee joint with subsequent improvement of the gait. Scissoring posture is one of the important problems in CP which also can markedly be decreased by BTX injection of adductor groups. Another muscle also injected in lower extremities is iliopsoas for spastic hip flexor; unfortunately, later on, it is difficult to be injected by palpation and needs technical equipment like ultrasound guidance for accurate injection [28, 29].

Although the primary goal of BTX injection to the lower limb is to improve ambulation in CP, BTX has an additional benefit; for example, injection of adductor and hamstring muscles may prevent progressive hip subluxation with positional improvement and decrease pain and stiffness, particularly when combined with bracing of the hip in abduction. Moreover, the benefits in nonambulatory patients may have improved pain and stiffness after injection and easy caring by relaxing adductor group. **Table 3** shows BTX injection of lower extremities.

For optimizing relaxing effect of BTX-A, proposed high dose evolved. A lot of debate in last decade about safety of high dose of BTX-A. Generally, high doses adopted per injected muscle and multiple injections to many muscles in the same session have been used. The dosage of BTX-A per muscle depends on many factors including muscle bulk, degree of spasticity, and pathological pattern of the involved muscle. High dose of BTX-A is restricted to large muscle volume with sever spasticity. Many of spastic CP patients need multiple injections in same session to obtain maximum result [32].

The concept of high safe dose of BTX-A had been grown since the use of toxin. Initially, the toxin restricted for treatment of patient with focal spastic deformity is now widely used in multilevel therapy as the spastic CP patients have abnormal posture on multilevel of the musculoskeletal system; in consequence high dose is needed.

It is recommended to start with the lowest effective dose and increase with consequence injection depending on the previous session response and side effect. A wide range of total doses are found in review of literature, ranging from 2 to 29 U/kg/bw. As the initial use of BTX-A for equinus correction, the commonly referred dose range from 4 to 8 U/kg/bw can be found, while in the multilevel use of BTX-A, adopted higher dose with maximum doses ranged from 10 to 29 U/kg/bw. A dose up to 40 U/kg/bw was used within multilevel injection of BTX-A. In one study [33]. Subsequent studies stated that high dose of BTX-A is safe to some extent. In review of literature with the multilevel use of BTX-A and multisite injection on monkeys, [34] conclude that there were no observable systematic effects at doses below 40 U/kg/bw (**Table 4**) [34].

Muscles injected	Dose range (IU/kg of bw)	Number of sites
Tibialis posterior	1–3	1
Soleus	2–3	1
Gastrocnemius	3–6	1–2
Adductors	3–6	2
Lateral hamstrings	2–3	2
Medial hamstrings	3–6	3–4
Quadriceps	3–6	4
Iliopsoas	2	2

Table 3. Muscle injected, dose, and number of injection of lower extremities [30].

	Botox	Dysport	NeuroBloc/Myobloc
Range maximum dose/site (U)	10–50	50–250	Not established
Maximum total dose (U)	400 (−600)	500–1000	Not established
Range (U/kg bw)	1–20 (25)	1–20 (25)	Not established

Table 4. Usual maximal dose of botulinum toxin preparation.

Of note, one has to put in his mind that the muscle like sponge principle pattern when exceed maximum contains fluid, leak from muscle could occur, and toxin enters the general blood circulation causing distant side effect which might be serious and life-threatening. That's why we advise to use multisite theory, in which the dose has to be divided between more sites, with an up to a maximum of 25–50 U per site and not exceed in a volume of 1 ml per site, in addition to an inter-site distance of a minimum of 4–5 cm. As an interesting issue, for those who are obese, adjust the dose to the reference of their typical pairs with same age.

3. Postinjection BTX period

Although its maximum effect appears at 10 days to 4 weeks, the relaxing effect might start within 1–3 days and usually last for 3–6 months with exception of some patient for over a year called golden responder. Proper multidisciplinary team in terms of splinting, physiotherapy, and casting improve the outcome and increase golden responder patient numbers. Many centers adopt serial casting after significant relaxing effect of BTX that started and lasted for 2–3 weeks after injections may optimize the benefit of injection [35].

3.1. How to localize muscles for botulinum toxin injection?

The child is not a small adult, generally uncooperative and sensitive to pain, and doesn't like any technique that involves restriction of his movement for a long while. Therefore, invasive procedure like EMG is more difficult to be applied successfully in children than in adults.

3.2. Palpation

Palpation of the muscle, particularly for the large one, remains the cornerstone for injection of BTX in CP patient for most experts worldwide, but it needs a well of knowledge in anatomy and its landmark. If possible after injecting the needle to the target muscle belly by using anatomic landmarks, palpation of the muscle, movement of distal joints that involve the target muscle, and then movement of injecting the needle confirm correct needle position.

In a study comparing manual needle injection and needle injection guided by electrical stimulation, 226 spastic CP children are involved with 1372 separate injections for upper and lower extremity spasticity. A 27-gauge insulated Teflon-coated needle was used to stimulate the muscle and deliver BTX-A contraction of the target muscle without contraction of the neighboring muscle. Then, needle position must be considered correct. The study concludes that

needle placement guided by electrical stimulation is highly recommended for injections into small, slender, and deep-seated muscles, but dropout of such procedure needs cooperation which is difficult in children, so it is usually done by general anesthesia which could cause relaxing muscles and palpation of the target muscle become difficult [31].

BTX-A injections into 15 different muscles of 100 outpatients in cross-sectional study treatment sessions were performed. All patients received combined analgesia and sedation with chloral hydrate prior to their BTX-A injections. Target muscles included small muscles of the forearm as well as large muscles of the lower extremity. Target muscles were identified based on anatomical palpation, and after the use of different tools, we conclude that injection of BTX with palpation results from significant improvement in ambulation [36].

3.3. EMG

There are two electrophysiological techniques to localize muscles: electromyography (EMG) and electrical stimulation [5, 37]. In a randomized, controlled clinical study, 28 patients with cervical dystonia received EMG-guided BTX-A compared with other patients using manual palpation-guided BTX injection. The study concludes that significant improvement to those patients that are guided by EMG for their BTX injection, specially patients with retrocollis, laterocollis, and shoulder elevation suggests great benefit from EMG-guided injection for deep cervical muscles [38] but unfortunately is inapplicable in spastic CP because EMG needs active and/or passive muscle stimulation for targeting muscles from neighboring muscles as long as spastic CP had difficulty to perform specific movements [39]. In addition needle EMG painful procedure limited its use in children; moreover, there is inaccurate correlation between the extent of spasticity in dystonia and the muscle activity detected by the EMG.

3.4. Electrical stimulation

Although electrical stimulation is considered an excellent procedure to localize the needle in the muscles [40], its use in children is imitated due to the localizing target muscle that needs multiple reposition of the needle which needs time and cause significant pain. Therefore, if electrical stimulation is necessary, we need good analgesia with sedation; moreover, the effective use of electrical stimulation needs expert personal in neurophysiology and clinical anatomy.

3.5. Ultrasound

As an alternative to the above procedure, ultrasound is considered applicable and can directly visualize the muscle for injection. This procedure has been considered a successful method for anatomical muscle imaging, and there are many literatures concluding the use of ultrasound as a reliable technique for botulinum injection [41–43].

3.6. Evaluation and assessment of botulinum toxin injection in spastic cerebral palsy

The use of any parameter for assessment of post BTX-A injection based on the patient clinical situation for whom BTX-A indicated and what expected gain and accordingly appropriate

parameter tailored to patient, for instance, in nonambulatory patient, the usual goal to improve his care is by decreasing spasticity. Therefore, the choice measure to assess tone, while ambulatory patient we choice parameter that related to gait as our goal to improve his gait, etc. Therefore, the setting of evaluation, including pre- and postinjection of BTX-A is individualized according to the goal of intervention; in addition to clinical examination, there are many tools used for this purpose, including the range of motion of the joints passively and actively; assessment of contractures by many tests, e.g., Thomas test, popliteal angle test, Silverskiöld test, and Duncan-Ely test; assessment of muscle power and imbalance, e.g., MRC, Janda, and Oxford scale; assessment of gait by gait analysis equipped by videotaping [44]; and goal attainment scale (GAS) [45, 46]. Modified Ashworth Scale (MAS) is simple and reproducible in the assessment of muscle spasticity but is probably of limited validity [47, 48]. Modified Tardieu Rating Scale is more reliable and is focused on most clinically relevant parts of the Tardieu Scale [49, 50]. Gross Motor Function Measure (GMFM) is a validated tool for the measurement of motor function in children with CP [51, 52]. It may, however, not be sensitive enough to detect the minimal changes that occur following relatively minor interventions. Upper limb assessment tools, e.g., SHUEE and AHA scores or PEDI [53, 54], Activities Scale for Kids (ASK), only applicable to children aged 5–15 years [55], and gait analysis with three-dimensional assessment are extremely useful tools with objective analysis of gait before and after toxin injection and also useful in surgery intervention. Moreover, nowadays, the three-dimensional gait analysis became indispensable in clinical studies of gait [48, 56]. However, application of these assessment tools in everyday clinical practice may be limited by cost and availability.

Full detailed checklist for every child planned for BTX-A injection includes identity, goal of injection, last session date, side effect of the previous injection, muscles injected, doses, and assessment tools used.

3.7. Clinical decision of botulism toxin injection and its limitation

Spasticity is considered a positive phase of muscle function. Therefore, when relaxing the muscle, the patient might get worse functionally in some instance. So, the first question clinician put in his account before injecting BTX is whether hypertonia is impeding or improving function. Another thing is that spasticity itself is associated with weakness and its high muscle tone may be a consequence to avoid involuntarily weakened muscle movement. For the time being no tools like EMG and gait analysis accurately provide obvious data related to hypertonia, and the clinical decision remains the cornerstone [57, 58]. Therefore, general functional and development assessment are considered the most important, while individual muscle assessment and using parameter, e.g., the Modified Ashworth Scale, Modified Tardieu Scale, or range of motion, are less important than general functional impairment assessment. As it is well known that spastic CP management needs a multidisciplinary team, hence it is crucial to determine the goal of management with periodic assessment for outcome with frequent modification of treatment in order to tailor appropriate management to every patient.

Although there is general consensus that recovery from BTX-A injection is always complete and seems effective and safe, nevertheless there is no data till now about long-term effect and dropout. For that reason long-term studies are mandatory.

BTX-A is a neurotoxin spread or injected to nontarget muscle that might cause further suffering to the patients and therefore should be done by a well-trained personnel who familiar with BTX and muscle anatomy.

Many causes for inadequate outcome like false indication, incorrect injection, and lack of complementary treatment (physiotherapy, occupational therapy, orthosis, etc.) are most common.

3.8. Adverse side effects of botulinum toxin

Generally, the adverse side effects of BTX-A are seldom to occur providing that the physician strictly adheres to the dose ranges and reinjection period [16]. The side effect may be local or distant from the injection site regarding local side effects, as with any intramuscular injection can cause pain, cause hematoma at the site of injection but usually not severe, and rarely cause significant problems. However, diffusion of BTX from the target injected muscle might cause weakness of neighboring muscles [28]. This is proportionally related to the volume of dilution; nevertheless, this diffusion is useful in injection of large muscle to optimize bulky muscle relaxation. Systemic side effects distant from injection site are rare and include double vision, dysphagia, generalized weakness of muscles, fluelike illness, constipation, and impaired bladder function, in CP patient with preexisting dysphagia. Further deterioration of bulbar muscle function might lead to aspiration pneumonia [28] which may be seriously life-threatening in such patient. Antibodies to botulinum toxin are found in some patients after several injections. The antibodies may be responsible for the tolerance to BTX developed by some patients [59, 60].

4. Conclusion

Botulinum toxin had established its significant role in management of spastic CP combined with other modalities of treatment. Most experts recommended it for use after 2 years of age for spasticity; in contrast untreated spasticity might lead to joint contracture, and the management may become difficult with multiple surgical interventions. Multilevel injection therapy is indicated to improve gait as most of spastic CP patients have multiple malposition of musculoskeletal system. The inter-injection period must be at least 12 weeks to avoid antibodies and ensure subsequent effect. So far, BTX-A is considered to be safe to some extent if used professionally; however, long-term adverse effect particularly with multilevel therapy is still not clear.

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