Are botulinic toxin injections useful in the treatment of upper limb disorders in children with cerebral palsy?

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I. Introduction

Cerebral palsy (CP) describes a group of permanent disorders of movement and posture, causing activity limitation, that are attributed to nonprogressive disturbances that occurred in the developing fetal or immature brain [1]. It has a prevalence of about 2 per 1,000 births [2]. The term cerebral palsy consists of many etiologies, with prenatal (75%) and peri- or postnatal (10-18%) risk factors [3]. Practically speaking, subtypes of CP are differentiated according to the anatomical and motor localizations of the impairment (hemiparesis, tetra-paresis, paraparesis, etc.) and the associated neurological syndrome (spastic, ataxic, or dyskinetic) [2]. Although many neurological syndromes may be associated, spastic CP Is the most frequently encountered subtype and includes around 80% of patients with CP [4]. Spasticity is a motor dysfunction characterized by a velocity-dependent increase of the stretching reflexes (muscle tone) with exaggerated muscle contractions (phasic stretching reflex) due to a hyperexcitability of the stretching reflex [5]. The motor deficit, to which is compounded the spastic hypertonia, places limitations on the activity of the upper limbs, thus leading to restrictions in the participation in society in the different domains (playing, school, physical activity, etc.). In fact, upper limb spasticity along with tendon retractions will lead to progressive restrictions in joint range of motion leading to shoulder internal rotation (spasticity of the internes rotators of the shoulder), elbow flexion (spasticity of the brachialis and biceps), wrist flexion (spasticity of carpal and finger flexors) and pronation (spasticity of the pronator quadratus), and finger flexion contractures, as well as a thumb-in-palm deformity with limited abduction (spasticity of adductor pollicis brevis, longus, and opponens pollicis). These deformities may be aggravated by a disequilibrium between synergistic and antagonistic muscle co-activation (these muscles may be spastic, paretic, or normal), and more particularly in children due to an asynchronous growth of the bones and the muscles.

From its first use in the late 1980s in the upper limb in a young adult patient with CP [6], the use of botulinic toxin A (BTX-A) has progressively increased and is now routinely used in clinical practice for the treatment of spasticity in children with CP, both of the lower limbs and/or the upper limbs. The mechanism of action of BTX-A is now well known and includes inhibiting acetylcholine secretion at the neuromuscular junction, thus inhibiting muscle contraction, and decreasing muscle spasticity.

To this day, there are no recommendations from international, national, or scientific communities concerning the use of BTX-A in upper limb disease in children with CP.

II. Botulinic toxin A treatment goals

Botulinic toxin injections at the level of the upper limbs must meet certain well-defined and previously established goals with the patient and their families. These goals primarily include:

1) Improving function (e.g., grasping), specific tasks (e.g., holding a bowl of yogurt), or movement (shoulder rotation, elbow flexion/extension, wrist flexion/extension, thumb abduction/adduction, finger flexion/extension, release/grasp, etc.)
2) Reducing pain, especially musculotendinous
3) Facilitating nursing, bathing, dressing, movement (molded seating)
4) Improving aesthetics (self-esteem)

III. Assessment tools

Multiple tools have been created to quantify spasticity and its consequences. These tools are separated into deficit assessment, qualitative motion analysis, and activity limitation analysis. Tools for the assessment of participation restriction are lacking. The Modified Ashworth Scale (MAS) and the Tardieu scale (and modified Tardieu scale) are the most frequently used tools for the assessment of spasticity [7]. Certain scales making use of clinical goniometry (measurement of joint range of motion) may be used to evaluate the angle at which hypertonicity appears, its variability with muscle stretching, and to estimating Musculo-tendinous retractions. Beyond spasticity, an assessment of upper limb muscle strength based on a dynamometer allows the assessment of residual muscle control (e.g., grip). The assessment of the functional impact may be done by a large panel of scales that are summarized in table 1.

IV. Literature analysis

Answers to the following questions may be found in a literature analysis:

A- Injection technique
B- Effects on spasticity
C- Effects on pain
D- Effects on function

E- Combination with associated therapies
F- Combination with surgery
G- Side effects
H- Limitations

A. Injection technique

The most frequently used product is Botox, abobotulinumtoxin A (Allergan, Irvine, USA), the dosage of which depends on the child's weight and the injected muscle. The use of Dysport, onabotulinumtoxin A, (Ipsen Biopharm, Wrexham, UK) seems to be increasing due its higher concentration requiring lower injection volumes. A recent literature review showed a higher efficiency (increased MAS) at 16 weeks post-injection as well as a lower cost with the use of Dysport compared to Botox [8].

The intra-muscular injection site may be localized via anatomical landmarks through muscle palpation, ultrasonographic guidance, and/or electrostimulation [9]. Muscle palpation for the localization of the injection site seems especially difficult in deep, short, and thin muscle groups, especially in younger children. Electro-stimulation is a reliable localization technique in children, but requires experience with electrophysiologic techniques, as well as proper knowledge in anatomical landmarks. This technique should be used with adequate analgesia and sedation. Ultrasonographic guidance is progressively becoming the gold standard due to its reliability and reproducibility and seems to be less painful and stressful for patients. The use of electromyograms is not recommended in children.

1. At which dose?

Kawamura et al. published a study comparing two groups of patients, one of which received the regular recommended dose (e.g., Biceps at 2 UI/Kg), and a group that received only half of the recommended dose [10]. No significant differences were found in terms of joint mobility or functional outcome (PEDI, QUEST, GAS) at 1 and 3 months after injection of BTX-A. Lowe et al. compared the results of two groups, one of which received a high-concentration low-volume Botox injection (e.g., Biceps at 4 UI/Kg) along with ergotherapy, and another received only ergotherapy [11]. The authors showed that the quality of the movements was better, faster, and with a higher range of motion at 1 and 3 months in the group receiving Botox injections [11]. However, due to the lack of a control group, these results should be interpreted with caution. Delgado et al. evaluated three different doses of Dysport (2 UI/Kg, 8 UI/Kg, and 16 UI/Kg) and found better outcomes on the Physician Global Assessment scale and an improved MAS at 6 weeks after the first injection in the groups receiving 8 UI/Kg and 16 UI/Kg. Long-term outcomes showed no statistically significant differences between the groups.

In a phase III international multicentric study, Dimitrova et al. compared two groups receiving 3 UI/Kg and 6 UI/Kg Botox injections, respectively, with a control group [12]. They found no dose-dependent differences in terms of spasticity or functional outcome.

Studies on the use of Dysport – which has a higher concentration – and Botox, did not show better clinical outcomes for highly concentrated products. Furthermore, it has been shown that the number of neuromuscular junctions for each muscle is constant and does not increase with age, thus suggesting that increasing the concentration of the toxin with the patient's age would not be useful [13,14].

2. How often?

The duration of action of BTX-A is on average 10 to 16 weeks, with a maximum response at 15 days post-injection. Different studies have evaluated the effects of two or three injection cycles with an average 17 to 19 weeks and 6 to 18 months between cycles, respectively [15,16]. The analysis of different injection protocols has shown that repeat injections sustained the therapeutic benefits [15,16]. Patients who had undergone more than one injection showed better outcomes on multiple scales compared to those who had only one injection. Conversely, no significant differences were found between patients who had undergone two or three injections [6,16].

3. At what age?

The analyzed studies included patients from 2 to 23 years of age. In France, the use of BTX-A is authorized after the age of 2 years. Only a single study compared the clinical results of children with a first injection before the age of 7 years to those after and showed decreased joint mobility with more severe deformities in the group that had received their first injection after the age of 7 years [17]. Although these results should be interpreted with caution, repeat cycles of spasticity treatment for the upper limbs starting from a younger age seem to aid in limiting the neuro-orthopedic consequences of spasticity on the upper limbs.

B. Effects on spasticity

Owing to the pharmacodynamics of the chemo-denervating role of BTX-A, a decrease in muscle tone would be expected in the short term.

Russo et al. found a significant improvement on the Tardieu scale in the group receiving BTX-A injections compared to the control group, with a gain in the angle of catch at the level of the elbow of 75.7° at baseline to 9° and 39.5° at 3 and 6 months post-injection, respectively, and at the level of the wrist of 95.9° at baseline to 15° and 31° at 3 and 6 months post-injection, respectively [18]. Olesch et al. found a significant difference on the modified Tardieu scale at 12 months post-injection after 3 cycles of injections compared to a group receiving BTX-A and ergotherapy, and a group only receiving ergotherapy on the pronators of the forearm and flexors of the wrist [19]. Dimitrova et al. observed a significant improvement in muscle tone on the Tardieu scale and a significantly higher decrease in MAS in the groups receiving 3 UI/Kg and 6 UI/Kg compared to a placebo group from 4 weeks post-injection at the level of the elbow and wrist [12]. Dursun et al. found a significant decrease in MAS after BTX-A treatment at 4 and 12 weeks, as well as a decrease in spasticity and angle of arrest [20].

Wallen et al. compared four groups (BTX-A + ergotherapy, only BTX-A, only ergotherapy, control) and found a significant decrease in muscle tone in the groups receiving BTX-A compared to the other groups, especially on the elbow flexors and forearm pronators [21]. The studies by Kawamura et al. did not show any differences in MAS based on different concentrations of BTX-A between baseline, at 1 month, and at 3 months post-injection [10]. Ferrari et al. did not show significant differences in MAS measures between BTX-A and placebo groups [22].

Speth et al. did not show and reduction in muscle tone or increase in active joint range of motion but included only a small sample size [23].

Fehlings et al. did not show any modifications in MAS between a group receiving BTX-A and ergotherapy and a group receiving only ergotherapy [24].

Kawamura et al. did not find any significant differences in terms of range of motion (elbow extension, supination, wrist extension, and thumb abduction) in different concentrations of BTX-A at baseline, at 1 month, and at 3 months post-injection [10].

Koman et al. did not find and significant differences when comparing a group receiving BTX-A injections and a placebo group in upper extremity rating scales, whether it was at the level of the shoulder, the forearm, and the hand, and at 8-, 20-, and 26-weeks post-injection [6]. Conversely, in the group receiving BTX-A, a significant increase in joint range of motion was found at the level of the wrist 20 and 26 weeks post-injection, especially wrist extension at 26 weeks [6].

Lidman et al. found a significant increase in active supination of more than 10° with a median of 43° in the group receiving BTX-A and ergotherapy at 1 year post-injection, but also in the group receiving only ergotherapy, with a median of 47°; their results are similar to a previous study undergone in 2015 [25].

Rameckers et al. found a significant increase in wrist active range of motion, and a decrease in the Ashworth scale of the wrist and elbow between baseline, 3 months, and 6 months post-injection. However, no significant differences were found between the groups with or without BTX-A injection [26]. Wallen et al. showed a significantly higher increase in active supination in the group receiving BTX-A and BTX-A with ergotherapy compared to a placebo group at 6 months post-injection [21].

In conclusion, outcomes from different publications remain varied in terms of spasticity and range of motion. Yet, there seems to be tendency toward a decrease in muscle tone, especially in the studies by Dimitrova who had a larger cohort. Nevertheless, these nuances may be explained by the differences between MAS and the Tardieu scales, since MAS does not take into account the angle at the start of stretching which may vary depending on the movement, function, or task, with similar score given for spasticity.

C. Effects on pain

To our knowledge, there are no studies evaluating pain before and after injection of BTX-A for spasticity and musculo-tendinous retractions, although it would seem that BTX-A is frequently used in clinical practice to control pain at the level of the upper limbs in children with CP.

D. Effects on function

1. Muscle strength

The use of BTX-A as a neuromuscular junction inhibitor could potentially lead to a reduction in spasticity, with the caveat of reducing muscle strength at level of the injected muscles.

Grip strength was evaluated by Fehlings et al., a study in which lower values were found between BTX-A and control groups without reaching statistical significance [24]. This tendency toward loss of muscle strength returned to normal within six months [24]. The study by Kawamura et al. showed similar results, with a loss in grip strength during the first three months after injection, even with lower administered doses (Group low dose / high dose) [10]. This reduction in strength was not correlated to a loss in function [10].

Raemecker et al. also found a decrease in muscle strength which improved after rehabilitation, although muscle strength at 6 months remained lower than patients who were undergoing rehabilitation without toxin injection [27]. Elvrum et al. suggested that rehabilitation and muscle strengthening exercises for both agonist and antagonist muscles compensated this decrease in strength [28]. In fact, this study showed significant improvements in grip strength compared to the control group for all forearm muscle groups, except for pronators [28].

2. Quality of movement

Apart from spasticity, the quality of the movement is one of the primary goals allowing improvements in the functionality of the upper limbs. Botulinic toxin injections seemed to improve the quality of the movement compared to placebo; Nevertheless, Corry et al. suggested that there may be a certain alteration in fine motor function [6,21,23,29]. These injections were realized independently from the rehabilitation program. In fact, if used by itself, physiotherapy in most cases improved the quality of movement. However, most studies published have shown better results when combining physiotherapy with botulinic toxin injections on the quality of movement [6,11,18,9,21,24,30], with only three studies not showing any advantages [23,26,27].

It should also be noted that improvements in quality of movement do not necessarily reflect improvements in spasticity, joint ranges of motion, or even activity. Finally, two studies evaluated improvements in quality of movement based on BTX-A dose and supported the use of lower doses (3 UI/Kg), since no differences were found between low and high doses [10,12].

3. Activities of daily living

The ultimate objective of BTX-A injection in CP depends on the child's specific goals by increasing their participation activities of daily living (body care, feeding, etc.). Although these studies do not show any improvements in spasticity, joint ranges of motion, muscle strength, or quality of movement, they frequently highlight improvements in terms of participation in activities of daily living (Pedi, COPM, GAS) [11,18,19,21,30,31]. As a result, these types of evaluations are paramount. This reinforces the fact that BTX-A injections should target certain objectives that are previously agreed upon.

4. Quality of life and aesthetics

There is a lack of studies showing that botulinic toxin injection improves the quality of life of children with CP [6,18,21]. Two studies evaluated the aesthetic aspects and showed an improvement 1 year post-injections [18,29].

E. Combination with associated therapies

Multiple associated therapies exist and could be combined in different manners.

- Grip and movement organization, hand-eye coordination, bilateral coordination, body image, fine and gross motor control, use of supporting materials (ergotherapy).
- Reducing spasticity, stretching of the muscle-tendon unit, reducing co-contractions, segmental motion (physiotherapy).
- Constraint-induced movement therapy based on the principle of neuroplasticity and the potential for cerebral remodeling (ergotherapy). This therapy involves constraining movements of the less-affected arm while encouraging the use of the spastic limb.
- Bimanual upper limb therapy (ergotherapy and physiotherapy).
- Day- and night-time bracing (prosthetist).
- Serial casting (physiotherapy and physician/surgeon).

Reducing spasticity and muscle tone with BTX-A injections allow an optimization of associated therapies (especially splints and casts), with the latter being used to increase muscle belly and/or tendon length [21].

Dursun et al. reported improved spasticity (MAS, Tardieu) when injections with BTX-A were associated with casting and ergotherapy compared to a control group (BTX-A + ergotherapy) at 4 and 12 weeks post-injection [20].

Associated therapies are thus imperative in order to stimulate the child to keep using their upper limb spontaneously and to maintain their neuro-orthopedic capabilities (limiting tendon retractions).

F. Combination with surgery

One of of the primary goals of BTX-A injection is to delay surgery [32]. BTX-A injections may be used in preparation for the future surgical intervention.

- Selective dorsal rhizotomy is indicated in patients with spasticity without muscle contractures, or as a combined procedure with muscle lengthening procedures to treat a coexisting contracture. It is especially useful in young children in whom definitive surgery cannot be undertaken. Due to the permanent nature of the rhizotomies, BTX-A injection may be used beforehand to assess the expected outcomes after rhizotomy. Selective dorsal rhizotomy reduces spasticity for a longer period than BTX-A injections.
- Surgical procedures combining tendon transfers and/or arthrodesis may be suggested in older children. Muscles with fibrous scarring do not respond well to tendon transfers and have, for the most part, decreased muscle strength. Attempting a BTX-A injection along with a dynamic EMG are complementary to the physical exam and help in determining whether a spastic muscle may be suitable for transfer. Van Heest et al., in a level II prospective study, compared three groups of patients (surgery vs. BTX-A + ergotherapy vs. only ergotherapy) [33]. Patients in the surgical group were operated of a quadratus pronator release, transfer of flexor carpi ulnaris to the extensor carpi radialis, and a pollicis adductor release. They found significantly improved outcomes in the surgical group in terms of grip strength, dynamic positioning of the limb during functional tasks as measured by the Shriners Hospital Upper Extremity Evaluation tests and dynamic positional analysis, and participation and satisfaction measures on the COPM [33].

G. Side effects

Side effects vary according to the studies, ranging from 0 to 200%, but are minor in most cases. The most frequently encountered side effects include:

- Pain at the site of injection
- Transient muscle weakness
- Intramuscular hematoma
- Botulism-like syndrome
- Muscle pain and stiffness
- Loss of strength
- total muscle weakness

H. Limitations

To this day, there are but very limited contra-indications to BTX-A injection. They are not recommended in children with baseline muscle weakness, e.g., in patients with muscle dystrophy, myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis, mitochondrial pathologies, or predominant dystonia. Also, their use does not seem pertinent in case of fixed joint stiffness with muscular fibrotic tissue replacement and joint deformities.

I. Discussion and conclusion

Botulinic toxin-A injections are frequently used in daily practice for the treatment of children with CP in the absence of clearly established recommendations. The results of this literature review and the analysis of our personal experiences open a discussion on the role of BTX-A in the treatment of functional disorders of the upper limb. Contrary to the lower limbs where gait is an automatic function, gripping requires much more complex motor pathways. The outcomes of BTX-A injection on spasticity and muscle tone are varied.

The reduction in spasticity is not automatically correlated to an improvement in manual competencies. The reduction of spasticity is only pertinent when the latter limits the gripping ability in activities of daily living.

Functional outcomes are also often either non-significant or disappointing, although there seems to be a tendency toward improvements in terms of participation in activities of daily living.

As such, patients receiving BTX-A injections should be carefully selected, with the aim being problems affecting activities of daily living or physical consequences of spasticity. The use of BTX-A should answer to a reasonable functional or specific neuro-orthopedic goal predetermined by the child, their parents, and the circle of care. BTX-A injections could also be used as a complement to orthopedic treatments (casts, braces, etc…) and/or surgery.

These BTX-A injections are generally well-tolerated, with the most frequent side effects being pain at the site of injection and a transient loss of strength. The analysis of published results remains challenging due to the limited number of high level of evidence publications (of which most were conducted by the same team), the small sample sizes, the heterogeneity of the populations, the varied assessment tools, and the short and midterm results.

Although formally answering the question “Is botulinic toxin injection useful in the treatment of upper limb disorders in children with cerebral palsy?” may be possible, BTX-A injections should be used in children with upper limb disorders while awaiting more substantial multicentric pilot studies using validated scales, and notably pain assessment scales and quality of life questionnaires.

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Questions

Upper limb involvement in children with cerebral palsy includes essentially:

A. elbow extension
B. wrist flexion
C. shoulder external rotation
D. finger extension

Answer: B

Botulinic toxin injections may lead to:

A. increased secretion of acetylcholine
B. decreased spasticity
C. increased muscle strength
D. numerous complications

Answer: B

Botulinic toxin injections in children:

A. may be used as of 12 years of age
B. are contraindicated in children
C. are only done under general anesthesia
D. are authorized after 2 years of age in France

Answer: D

Tool	**Age**	**Application**
1-QUEST (Quality of Upper Extremity Skills Test)	After 18 months	Uni- or bilateral deficits
2-AHA (Assisting Hand Assess-ment)	18 months - 12 years Mini AHA: 8-18 months Ad-AHA: > 13 years	Unilateral deficits
3-Melbourne assessment	2.5-15 years	Uni- or bilateral deficits if limbs evaluated separately
4-House functionnal classification (thumb or hand)		Uni- or bilateral deficits
5-MACS	4-18 years	Uni- or bilateral deficits
6-Abilhand-Kids	Parents	Uni- or bilateral deficits Uni- or bimanual activity limitation
7-Pediatric Evaluation of disability inventory (PEDI)	6 months-7 years	Uni- or bilateral deficits Uni- or bimanual activity limitation
8-Canadian occupational performance Measure (COPM)	0 and + (Parental evaluation)	Unilateral deficits Uni- or bimanual activity limitation Perceptive measurement
9-Goal Attainment Scaling (GAS)	0 and +	Unilateral deficits Uni- or bimanual activity limitation Perceptive measurement

Table 1: Descriptions of the primary scales used in the literature for the evaluation of the quality of movement (1-4) and of activities of daily living (5-9) in children with cerebral palsy with upper limb involvement.