Practical use of AbobotulinumtoxinA for the treatment of spasticity in children with cerebral palsy

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ABSTRACT

AbobotulinumtoxinA (ABO) has been used for the treatment of spasticity in children with cerebral palsy (CP). Its use requires careful administration, regarding dosing, selection of local of application, interval between applications and efficacy and safety monitoring. This was the first panel of experts on the treatment of spasticity, which developed a guide to provide an overview on important issues related to therapeutic strategies adopted by physicians using ABO, including its dosage to be applied per muscle. Treatment should be initiated as soon as possible, ideally between two and six years of age. A clinical evaluation should identify muscles with spastic activity, and determine the desired outcome: improvement of function, esthetics/aspect, pain treatment, easing care and positioning, preventing hips dislocation, improvement of walking and posture, and to provide conditions for education and social participation. Pre-requisites to achieve good results are adequate muscle selection, adequate ABO dosage and exact injection technique. Many common pathological patterns can be adequately treated if several muscles are simultaneously injected in a single treatment session; planning ABO dosage per muscle should consider the maximum dosage in units per muscle and the total maximum ABO dosage per session (30 U/kg patient´s body weight, not exceeding 1000 U). After application, children should be submitted to physical therapy and occupational therapy, focused on home therapy, and family involvement, increasing chances of therapeutic gain. Treatment with ABO is multidisciplinary and requires integrated approaches.

Keywords: Disabled Children Cerebral Palsy, Muscle Spasticity, Botulinum Toxins, Type A

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INTRODUCTION

Cerebral palsy (CP) is a common infantile clinical condition with an incidence of approximately 2 positive cases for every 1,000 births, or even 7 positive cases for every 1,000 births in the developing countries.[1]

As defined, CP comprises a set of permanent development deficits, with mobility and posture changes that cause activities limitations, due to malformations or non-progressive lesions of the developing brain that may occur before, during or after birth. The motor impairment of CP are frequently combined with sensory, perception, cognitive, communication, and behavioral disturbances, as well as epilepsy and secondary musculoskeletal problems.[2,3]

Regarding specifically the motor impairment, the lesion in the central nervous system directly causes changes in the muscle tonus and in the physiologic mechanisms of balance, with loss of selective muscle control and strength. As a response to these alterations, static muscle contractures, bone deformities, and permanent postural changes due to poor articular alignment are secondarily observed over time. Spasticity is the main cause of secondary problems.[4-7]

By definition, spasticity is a motor disorder characterized by hypertonia and hyperreflexia secondary to an increase in the stretch reflex response, directly proportional to the speed of muscle stretching. Spasticity is observed in approximately 90% of the children with CP.[4,5,8-10]

For evaluating the impact of spasticity, detailed assessment of the muscular system is required and it must comprise shoulder adduction, elbow flexion, forearm pronation, wrist flexion, thumb adduction and upper limb finger flexion, hip flexion with internal rotation, lower limbs adduction. Dislocation of the hips, knee flexion, and equinism are the most common deformities in the lower limbs, whereas scoliosis is the most common disease for those with wider neurologic implications.[11,12]

Given its mechanism of action, the Botulinum Toxin Type A (BoNT-A) is applied in the treatment of several medical conditions in which the muscle tone reduction is required, including spasticity. A varied range of clinical trials have evidenced its efficacy for pediatric patients with CP,[13] however, in the clinical practice, the use of BoNT-A requires careful administration concerning dose, injection site, time in-between applications, as well as the monitoring of its efficacy and safety.

The main objective of this guide is to provide an overview on important issues regarding the therapeutic strategies applied by medical doctors who administer BoNT-A, more specifically the abobotulinumtoxinA, for treating spasticity of children with CP.[14]

Botulinum Toxin

Botulinum toxin is produced by the bacteria *Clostridium botulinum* and it operates in the cytoplasmic matrix of the nerve endings to cleave the SNAP-25 protein. This protein is responsible for coupling and fusing vesicles containing neurotransmitters in the presynaptic membrane. The cleavage of SNAP-25 prevents the exocytosis of acetylcholine at the presynaptic termination of the neuromuscular junctions, resulting in reversible blocking of motor fibers and weakening of muscle contraction. Depending on the target tissue, it may block the cholinergic neuromuscular innervation of smooth and striated muscles or the autonomic cholinergic innervation of exocrine glands.[15]

Therefore, BoNT-A is widely used in patients with neurological impairment characterized by skeletal muscle overactivity (such as spasticity) by providing a targeted paralytic effect that lasts about 3 to 4 months.[14,15]

Currently there are three commercially available preparations of BoNT-A: abobotulinumtoxinA (ABO), incobotulinumtoxinA (INCO) and onabotulinumtoxinA (ONA).[14,15] All of them consist of the 150 kDa neurotoxin, which is responsible for the therapeutic effect, differing only in non-neurotoxic proteins which would be responsible for protecting the neurotoxin from degradation in the gastrointestinal tract.[15] Because of differences in molecular structures, formulations and purification methods, these preparations are not interchangeable and the dose recommendations are product specific, and the recommendations described herein refer exclusively to abobotulinumtoxinA.[6,16-18]

In pediatric patients, ABO is effective and safe when used at a dose of up to 1000 U per treatment session. Adverse events are rare and usually mild and transient, which can be minimized by the correct application technique, the total muscle dose, the dilution, and the dose interval between applications. In general, adverse events can be categorized as a focal, usually associated with the application (hematoma, swelling, pain) generalized and distal, related to the diffusion of the toxin to other muscles, causing weakness in adjacent muscles and, in rare cases, in muscles far from the infusion (e.g. ptosis, generalized weakness, fatigue, flu-like symptoms, urinary incontinence, dysphagia). Patients and caregivers should be warned about the possibility of adverse effects.[13,19,20]

The Gross Motor Function Classification System (GMFCS) was developed to evaluate the gross motor function of children with CP, and it ranges from Level I (patient walks without limitations) to Level V (patient is transported in a wheelchair and is dependent on all motor and transfer activities).[21] The morbidities associated with the clinical condition of the child should be taken into account in order to avoid the occurrence of more serious adverse effects, given children with more severe levels (GMFCS IV and V), besides the greater degree of motor incapacity, present a higher incidence of clinical complications.[22]

Botulinum toxin is contraindicated when there is infection at the site of injection, for patients with hypersensitivity to any component of the formulation or for patients with myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis or other disease that may interfere with neuromuscular function. The effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or any other drugs that interfere with neuromuscular transmission. The toxin is not indicated for patients below 2 years of age.[6]

When to treat

Children with CP represent a heterogeneous group of patients, and the intensity and incidence of neurological impairment vary significantly, demanding the treatment goals to be well defined and individualized.[16,23,24] The timing of the antispastic intervention is fundamental and should consider the child's development, the age and the magnitude of the neurological impairment. Usually, the treatment should be started, as early as possible, when gait and motor function are still flexible, for providing acquisition of motor function with tonus reduction. Treatment with ABO is reported as ideal between 2 and 6 years of age.[6,24]

The treatment planning should consider the identification of the spastic muscle by a rigorous clinical evaluation.[16] The most common indications are improvement of function, aesthetics/appearance, pain treatment, facilitation of care and positioning, prevention of dislocation of the hip, gait improvement and posture, besides providing conditions for education and social participation.[16,23,25]

Table 1. Recommended dose to be applied per muscle by a panel of experts on the use of ABO in patients with cerebral palsy

Muscle	Minimum dose (U/kg)	Maximum dose (U/kg)	Maximum dose (U)	Number of sites
Thigh adductors	5	10	300	1 to 3
Gracilis muscle	4	8	150	1
Medial hamstrings	5	10	300	2 to 6
Iliopsoas	2	5	200	1
Quadriceps (rectus femoris)	5	8	200	1 to 3
Gastrocnemius	5	12	300	2 to 4
Soleus	4	10	125	1 to 2
Tibial posterior	2	5	150	1 to 2
Pectoralis major	3	5	100	1 to 2
Quadratus lumborum	2	4	100	1 to 2
Triceps brachii	2	4	100	1 to 2
Brachialis	2	4	100	1 to 2
Biceps brachii	2	4	100	1 to 2
Brachioradialis	2	4	100	1
Pronator quadratus / teres muscle	2	5	150	1 to 2
Radial carpal flexor	2	4	100	1
Carpal ulnar flexor	2	4	100	1
Deep flexor of the fingers	1	4	100	1
Superficial flexor of fingers	1	4	100	1
Long flexor of the thumb	1	3	50	1
Short thumb flexor	0.5	3	30	1
Thumb adductor	0.5	2	30	1
Opponent of the thumb	0.5	2	30	1
Lumbar muscles of the hand	0.5	2	30	2

*Maximum dose per application of 30U/kg of body weight of the patient, not exceeding 1000U.

The treatment program should focus on reducing or normalizing tone to avoid development of secondary problems, and on preventing or delaying the need for surgical intervention.[4-6] Children with GMFCS IV and V are known to be more vulnerable to developing hip dysplasia and scoliosis/kyphosis, therefore radiography is mandatory for monitoring such patients.[6] The most common interventions are physiotherapy, use of orthoses, serial casting, electrical stimulation, oral medication, phenol, selective dorsal rhizotomy, intrathecal baclofen, and, in the last two decades, botulinum toxin.[4,6] These interventions may be indicated alone or combined, which is the most common approach.

In the evaluation to indicate ABO, the professional should carefully differentiate between dynamic (spasticity) and structural (contracture) components of movement limitation, since fixed contractions should be treated surgically.[5]

The success of treatment depends on the establishment of realistic and possible goals that are planned at the beginning of treatment and continuously revised during the treatment, whereas function should be continuously evaluated and measured to provide the family and / or patient with information on the effectiveness of the treatment.[16,24]

In order to assess spasticity, it is essential to detect the clinical pattern of motor dysfunction, to determine the patient's motor control and identify possible contractures at the functional level, with quantitative and qualitative indicators that measure spasticity (muscle tone) of gait, functional ability, including upper limb, and measure of functional independence, and health-related quality of life.[23,26,27]

There are several scales and tests to assess spasticity, but they are subjective and sometimes impractical. The Modified Ashworth Scale is the mostly used in Brazil given its reliability and reproducibility.[27,28]

Rehabilitation

In clinical practice, the introduction of ABO can often be integrated into existing treatment schemes with good communication among the various professionals involved.[5] Within the integrated approach, a multidisciplinary team is of great importance.

Any treatment intervention in children with complex neurological impairment should be addressed by specific objectives, with which the child, family members and involved health professionals should consent with.[16]

In addition, it is important to evaluate and avoid possible aggravating issues of spasticity that cause nociceptive stimuli, such as fractures, hip dislocation, presence of infectious processes, intestinal behavior and irregular bladder emptying, among others.

The guidelines defined by the AMB clearly define these aspects, guiding the treatment of spasticity according to the following principles:[29]

1. There is no treatment of definitive cure to the lesion;
2. The treatment is multifactorial and aims in reducing disability;
3. The treatment must compose a rehabilitation program;
4. The treatment time must be based on the functional evolution.

How to treat

When performing treatment with ABO, three absolute prerequisites must be considered to ensure good results: adequate muscle selection, adequate ABO dose and precise injection technique. In addition, other factors are also crucial, such as result of long-term care before and after injection, patient selection, time intervals between applications, adequate objective definition, and long-term outcome assessment.[6]

Clinical examination focuses on spasticity, range of motion, strength, and selective muscle control. Objective analysis of posture and movement allows specific description of the movement pattern at each joint and identification of the muscles with the pathological pattern and the treatment to be indicated or modified.[6] Many of the common pathological patterns in CP can be adequately treated only if muscles are treated simultaneously in a single treatment session.[6]

The main muscle concept (key-muscle) aims to maintain the option of treatment with the toxin for as long as possible, ideally throughout the child's development. In this concept, muscles at acute risk for contracture or even with initial contracture should be injected. In some situations, spastic muscles are not injected if high tonus does not compromise function, if there is no acute risk of developing contractures or if tonus allows compensatory mechanisms.[5,16] The goals of treatment are to reach the next motor pattern,

to allow the verticalization of the patient, and to obtain the best possible locomotion. If the child can walk, the intention is to maintain this function, improve and optimize mobility. In the case of stagnation at a lower motor level, the goal is to maintain, improve and optimize motor function at this level.[5,16,30]

The most frequently treated lower limbs muscles in cerebral palsy are gastrocnemius, adductors of the hips, hamstrings, posterior tibialis, whereas in the upper limbs the most frequently treated are biceps brachii, pronator teres muscle, flexors of the wrists and fingers and thumb adductor.

Following careful clinical examination with target muscle selection, it is recommended to plan the ABO dose to be applied, considering the maximum dose in units per muscle and the maximum total ABO dose per session (30U/kg patient's body weight, not exceeding 1000U).

Currently there is no guideline recommendation of the dose to be applied per muscle. The table 1 summarizes the doses used in clinical practice by the specialists who participated in the preparation of this guide. It is emphasized that the doses are based on the exclusive experience with ABO, with no suggestion and/or recommendation for conversion to another type of BoNT-A.

A precise injection technique is essential for ABO treatment, since incorrect positioning is reported as one of the main reasons for ABO's lack of response and reduction in its safety profile.[14,18]

In general, when the child is cooperative, the application can be done by the palpatory method, and the proper identification of the muscle can be facilitated by the spasticity itself and by passive and active movements that activate this compromised musculature. Such a method is useful for it is ease and does not require the use of apparatus to locate the muscles, but the applicator must have extensive training and deep knowledge of the muscular anatomy.[17]

Studies in children with CP have reported positive correlation between the effectiveness of ABO-induced selective neuromuscular blockade and the accuracy of ultrasound-guided injections, allowing rapid muscle identification, precise needle positioning, especially in deep muscle, and adjustment of the injection procedure in these patients.[14,31] The application can be performed in outpatient care except in very serious cases or lack of patient collaboration, and in children who demand multiple application sites where there is difficulty of collaboration and excessive discomfort.

Isolated assessment of muscle tone improvement may not show the secondary benefits associated with this change. To evaluate the ABO treatment, a specific assessment of spasticity should be used in conjunction with functional or quality of life improvements. The Goal Attainment Scale (GAS) is suggested.[32]

In the long term, some patients may develop a failure secondary to ABO treatment. Possible causes of secondary failures include the development of fixed contractures, lack of proper use of the affected limb, lack of adherence to physical therapies and the recommended use of orthoses, as well as the eventual development of ABO neutralizing antibodies.[17]

The patient's and/or caregiver's perception of the benefit of botulinum toxin should also be part of the assessment, and the Visual Analog Scale (VAS) can be used. Specifically for gait assessment, the Physician Rating Scale (PRS) has proved to be an easy, practical and validated tool.[33]

Post neuromuscular management

Patients should be regularly evaluated before and after injections so that the strategy of treatment can be continued and the objectives refined according to the clinical evolution of the patient.[14,17] It should be taken into account that the antispastic effect appears within 24 hours to 3 days after the injection and has a peak effect in 10 days to one month.[30]

In children with CP, serial casting and prolonged stretching are recommended for the treatment of non-fixed contractures after BoNT-A injection, but also muscular strengthening and directed motor training are suggested as adjuvant interventions to improve motor function.[14]

The ABO approach includes physiotherapy, occupational therapy, and family involvement techniques through training of caregivers so that there is repetition and consequent increased learning, what enhances the potential for therapeutic gain from kinesiotherapy.[34] Stretching, exercises and general counseling are also required to be prescribed.

Physical therapy intensification is recommended for the 12 weeks after application.[18] The home-based occupational therapy program for functional upper limb gains after application should also be suggested to the parents.[35]

CONCLUSION

ABO can be considered as a valuable treatment option for tone reduction and, therefore, spasticity in pediatric PC patients because it is effective (reduces muscle tone), safe at young age (over 2 years of age), reversible (the effect lasts approximately 12 weeks), selective, dose-dependent, and it allows combinations of treatments.[6]

Its application must be done by experienced professionals who must properly select the muscles and doses to be applied. The treatment objectives must be previously and clearly agreed with parents, to facilitate the objective and realistic evaluation of its effectiveness.[24]

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