

EFFECTS OF BOTULINUM TOXIN-TYPE A IN THE TREATMENT OF CEREBRAL PALSY IN CHILDREN

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Abstract

Cerebral palsy (CP) is a chronic disorder of movement and/or posture that presents early (before the age of 2) and continues throughout life. CP is caused by static injury (non-progressive damage to the brain before, during or after birth) to the developing brain. CP is a permanent disease which cannot be cured, but the consequences can be minimized. Spasticity represents a major neuromuscular problem in CP and the children can be hemiplegic, diplegic or quadriplegic. Botulinum toxin (BTX) is one of the most useful antispastic agents used as treatment for spastic CP in children.

The aim was to study the effects of BTX on motor function in children with different forms of spastic CP. Spasticity was clinically assessed using Modified Ashworth Scale (MAS). The results showed the efficacy of BTX in diplegia, hemiplegia, quadriplegia.

Rezumat

Paralizia cerebrală (PC) este o afecțiune neurologică caracterizată prin tulburări ale motilității și posturii care apar ca o consecință a unei/unor leziuni cerebrale non-progresive apărute în timpul dezvoltării prenatale, perinatale sau postnatale a creierului. La acest tablou clinic se asociază multiple comorbidități (epilepsie, retard psihic, tulburări de vedere, de auz, etc) care constituie elemente de gravitate în evoluția bolii. PC reprezintă o afecțiune cronică, care din nefericire nu poate fi vindecată, dar care printr-un tratament susținut (kinetoterapie, terapie medicamentoasă, tratament chirurgical, logopedie, terapie ocupațională, etc.) conduce la o ameliorare evidentă. Cea mai frecventă formă clinică de PC este sindromul spastic. Spasticitatea poate fi abordată într-un mod complex, atât prin terapie fizică, cât și prin terapie medicamentoasă. Între noile modalități de abordare terapeutică a sindroamelor spastice, administrarea de toxină botulinică reprezintă o modalitate tot mai folosită. Toxina botulinică tip A se administrează ca terapie medicamentoasă în tratamentul PC de tip spastic.

Scopul prezentului studiu a fost să evidențieze efectele toxinei botulinice asupra reducerii spasticității și implicit asupra îmbunătățirii funcției motorii la copiii cu diverse forme de PC de tip spastic. Evaluarea clinică a spasticității s-a făcut folosind scala Ashworth modificată (MAS). Rezultatele obținute au arătat eficacitatea tratamentului cu

toxina botulinică tip A când a fost administrată în diferite forme de paralizie spastică, cum ar fi dipareză spastică, hemipareză spastică, parapareză spastică.

Keywords: cerebral palsy, spasticity, botulinum toxin, modified Ashworth scale (MAS).

Introduction

Botulinum toxin A (BTX-A) is a potent neurotoxin produced by *Clostridium Botulinum bacterium* that causes reversible chemo-denervation by irreversibly binding to the acetylcholine receptor at the neuromuscular junction.

Clostridium Botulinum produces a complex mixture of proteins containing botulinum neurotoxin and several non-toxic proteins, such as haemagglutinin [1, 2]. There are seven different serotypes of the neurotoxin, named A to G. Although all inhibit the release of acetylcholine from nerve terminals, they vary greatly in their intracellular protein targets, potency and duration of effect [1, 3]. BTX-A is the serotype which has been most studied in terms of therapeutic application. BTX-B and BTX-F have also been used in clinical practice, but are less potent compared to BTX-A and have a shorter duration of action.

The neurotoxin is synthesized as a relatively inactive single-chain polypeptide with a molecular mass of 150 kDa which is then cleaved and hence activated, by proteases, into a 100 kDa heavy chain and a 50 kDa light chain, that remain linked by a disulphide bond. These proteases may either be endogenous which are present in some clostridial strains, or exogenous such as trypsin, which is used in the commercial production of neurotoxin. The presence of high percentages of un-cleaved neurotoxin in preparations of BTX may be related to the formation of neutralising antibodies [1, 4].

The botulinum neurotoxins bind via the heavy chain to specific external high-affinity receptors on the membranes of cholinergic neurones which are internalized by endocytosis. Here, the light chain binds with high specificity to proteins. The specific protein complex involved, a soluble (N-ethylmaleimide-sensitive fusion (NSF)) attachment protein receptor (SNARE) complex, mediates the fusion of neurotransmitter-containing vesicles with the synaptic membrane [1, 5]. The complex consists of synaptobrevin which is associated with synaptic vesicles, syntaxin and synaptosome-associated protein of molecular weight 25 kDa (SNAP-25). BTX-A destabilizes the SNARE complex by cleaving SNAP-25. Other BTX serotypes cleave different proteins within the complex [1, 5, 6, 7].

By preventing release of acetylcholine at the neuromuscular junction, BTX reduces muscular activity in a dose-dependent manner. Within four weeks, restoration of the turnover of the SNARE protein complex allows exocytosis of acetylcholine to resume. Nerve conduction is also re-established, initially by new axonal sprouting and elongation of the endplate and, eventually, by retraction of the new axonal sprouts [1, 8]. Clinically, this chemo-denervation with muscle relaxation lasts for 12 to 16 weeks. A follow-up period of longitudinal muscle growth and functional carry-over may last for six months or more [1, 9] depending on the pathology involved.

BTX-A, by acting at the neuromuscular junction to reversibly alter muscle tone and selectively functionally denervate muscle, is used extensively in disorders of muscle over-activity, such as facial movement disorders, limb and neck dystonias, and spasticity.

In the past two decades BTX-A has been transformed into one of the most useful antispastic agents.

Cerebral palsy (CP) is a broad term which describes disorders which affect an individual's posture, balance and body movement. Spastic CP is the most common way CP manifests, affecting from 70 to 80 percent of the patients diagnosed with CP. This type of CP causes hypertonia or muscle tightness. Spasticity can affect symmetrical parts of the body (diplegia), one side of the body (hemiplegia) or all four limbs (quadriplegia).

Materials and Methods

This paper presents the effects obtained in spastic CP patients after treatment with BTX-A. The patients were clinically reviewed for evaluation of spasticity before each BTX-A administration and 10 days after each injection. Clinical assessments before and 10 days following each injection included a Modified Ashworth Scale (MAS, Table I) measurement of spasticity [14, 15].

There have been selected 27 paediatric patients diagnosed with different forms (diplegia, hemiplegia, quadriplegia) of spastic CP who were ambulatory treated in Pediatrics and Pediatric Neurology Department of „Victor Gomoiu” Children Clinical Hospital. The study was approved by the Ethics Committee of „Victor Gomoiu” Children Clinical Hospital. For all the children in the study, the written consent was obtained from parents for using the medical data, ensuring also privacy and identity protection of the subjects.

Inclusion criteria: age 2 – 12 years, male and female, diagnostic of CP.

Exclusion criteria: severe spasticity, mixed forms of cerebral palsy, children who underwent orthopedic surgery.

Table I
MAS for grading spasticity

Score	Spasticity assessment
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion (ROM) when the affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

27 patients (12 females and 15 males) aged 2 to 12 years (mean 4.3 ± 2.41 years) having spastic CP involving different limbs (diplegia, hemiplegia, quadriplegia, Table II) underwent ambulatory treatment with BTX-A. The initial spasticity was 4 (maximum) according to MAS.

Table II
Pathology of the group

Diagnosis		No of cases
Cerebral palsy	Diplegia	7
	Hemiplegia	13
	Quadriplegia	7

The dose administered was 30 units/kg bodyweight after dilution of 500 units BTX-A (Dysport[®]) with 2.5 mL saline solution. The technique used for injection was the manual needle placement. The injection sites and the number of sites were determined based on physical examination. No oral antispastic medications were administered and no anesthesia was used for any injections. A simple sedative as diazepam was considered in all patients when injecting BTX-A because the injection may be a cause of distress. Repeated injections were supposed to be administered 3 months and 8 months after the first administration, with maximum three BTX-A injections

within one year observation period, but not all the patients could comply with the study protocol.

Results and Discussion

We studied the effect of BTX-A in spastic CP patients. The effect was clinically expressed by the reduction of the spasticity level.

The experiment started with 27 paediatric patients experiencing spastic CP. 5 patients (2 diplegia, 1 hemiplegia, 2 quadriplegia) with one injection and 6 patients (1 diplegia, 4 hemiplegia, 1 quadriplegia) lost to follow-up after first injection who didn't come to the hospital for further treatment were excluded from analysis. Thus only data from 16 patients (4 diplegia, 8 hemiplegia, 4 quadriplegia) who had two BTX-A injections were analyzed.

Descriptive statistics for the MAS score measured before first injection (T1), 10 days after first injection (T2), before second injection (T3) and 10 days after the second injection (T4) are presented in table III.

Table III
Descriptive statistics for the four measurements of MAS score

MAS Score	Mean	Std. Deviation	No of subjects
Before 1st injection	4.00	0.000	16
10 days after 1st injection	1.31	0.793	16
Before 2nd injection (3 months after 1st injection)	1.75	0.577	16
10 days after 2nd injection	0.81	0.655	16

The significance of differences between MAS score measured before and after BTX-A administration was tested using Analysis of Variance (ANOVA) for Repeated Measures. ANOVA for Repeated Measures calculates an overall statistic having an F distribution which is determined also by the associated degrees of freedom (df). The number of df is calculated as the number of repeated measures minus 1.

Within-subjects analysis taking in consideration the MAS score at T1 which was gradually compared with MAS at T2, MAS at T3 and MAS at T4, revealed an $F = 136.617$ and $df = 3$. This results correspond to a $p < 0.001$ which establishes a statistical significant decrease of spasticity after administration of BTX-A.

Due to statistical significance resulted from the global analysis of MAS score evolution data and whereas the MAS score was measured at

more than two time points, a further analysis was performed in order to conclude the pairwise statistical significance of the MAS score assessed clinically during treatment with BTX-A (Table IV).

Table IV
Pairwise comparison of the four MAS score measurements

(I) scor	(J) scor	Mean Difference (I - J)	Standard Error	p	95% Confidence Interval for Difference	
					Lower limit	Upper limit
T1	T2	2.688*	0.198	<0.001	2.085	3.290
	T3	2.250*	0.144	0.000	1.812	2.688
	T4	3.188*	0.164	0.000	2.690	3.685
T2	T1	-2.688*	0.198	0.000	-3.290	-2.085
	T3	-0.438	0.157	0.084	-0.915	0.040
	T4	0.500	0.204	0.162	-0.120	1.120
T3	T1	-2.250*	0.144	0.000	-2.688	-1.812
	T2	0.438	0.157	0.084	-0.040	0.915
	T4	0.938*	0.143	0.000	0.502	1.373
T4	T1	-3.188*	0.164	0.000	-3.685	-2.690
	T2	-0.500	0.204	0.162	-1.120	0.120
	T3	-0.938*	0.143	0.000	-1.373	-0.502

T1, T2, T3, T4 = repeated measurements of MAS score at different moments of time (before and after BTX-A injection)

I, J = letters that designate the first (I) and the second (J) members of all the possible pairs formed with the four measurements (T1, T2, T3, T4)

Standard error = standard deviation of the sample-mean's estimate of the population mean

p = probability of error in considering statistical significant difference.

Between the means of the two compared score measurements there is a statistically significant difference if the probability p is less than 0.05

*The mean difference is significant at the 0.05 level

The analysis concluded that MAS score at T1 differs significantly from MAS score at T2 ($p<0.001$), T3 ($p<0.001$) and T4 ($p<0.001$) and MAS score at T4 differs significantly from MAS at T3 ($p<0.001$). Although there is no significant difference regarding the assessment of MAS score at T2 and at T4, the clinical measurements regarding MAS score at T3 and T4 emphasized a good outcome ($p<0.001$) of disease consequences and the importance of BTX-A re-administration.

Conclusions

The use of BTX-A is an effective approach to the treatment of spasticity that improves the motor functions of children with cerebral palsy

(CP). BTX-A treatment had a positive effect found in low spasticity which was improved after each injection, no matter the form of spastic CP. A great benefit in the observation period was demonstrated by a significant decrease of modified Ashworth scale (MAS) score after the second injection compared with the score before the first injection. Significant decrease in dynamic component was clinically assessed.

We conclude that BTX-A has positive effects when administered in diplegic, hemiplegic and quadriplegic CP. Although it doesn't cure, the BTX-A provides support for a good management of disease in minimizing the consequences. The long-term effects of BTX-A injections in CP spasticity are yet unknown. However, a therapeutic plan including BTX-A administration must be continued with a kinesiology plan. Higher doses of BTX-A are safe in children and are well tolerated over time. There were no adverse reactions reported after treatment with BTX-A. The safety profile of the toxin appears satisfactory.

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