

Effect of rehabilitation on the long-term efficacy of botulinum toxin-A for spastic cerebral palsy

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Abstract. – OBJECTIVE: To investigate the long-term effects of botulinum toxin-A (BTX-A) nerve block on relaxation of spasticity in cerebral palsy.

PATIENTS AND METHODS: From June 2015 to December 2018, 52 children, aged 20-56 months, with spastic cerebral palsy were treated with BTX-A. The dose of BTX-A was selected based on the weight of the child and the modified Ashworth scale (MAS). The injection dose ranged from 45 IU to 150 IU (average 68.0 ± 31.6 IU). The muscle tone and motor functions of all children were evaluated before the block. The spasticity was measured using the MAS, and the motor function was measured using the Physician Rating Scale (PRS) and the gross motor function measure (GMFM). After two years, all children were re-evaluated.

RESULTS: No significant difference was observed between the trial and control groups in terms of age, weight, MAS, PRS, and GMFM measurements before the block ($p > 0.05$). The PRS and GMFM improved significantly in both groups after two years ($p < 0.05$). The PRS and GMFM in the trial group increased more significantly than those in the control group ($p < 0.05$).

CONCLUSIONS: The BTX-A block showed a long-term positive effect. Rehabilitation training after the block could help children to improve their motor functions.

Key Words:

Cerebral palsy, Spasticity, BTX-A, Long-term effect, Nerve block.

Introduction

Cerebral palsy (CP) is a common deformative disease in children^{1,2}. Spastic CP contributes to the largest proportion of CP cases, including approximately 60-70% of paediatric CP patients^{3,4}. Spasticity affects not only a child's normal motor development, but also causes complications such

as contracture, deformation, and pain⁵⁻⁷; therefore, curing spasticity is always an important objective of rehabilitation therapy for CP.

The measures for spasticity treatments include spasm-relaxing techniques, oral muscle relaxants, nerve block, intrathecal baclofen, surgery, and series plaster immobilization during rehabilitation training^{8,9}; among these measures, nerve block is the most frequently used option. At present, the most common drug used for nerve block is botulinum toxin-A (BTX-A). The BTX-A block is one of the most effective measures for treating spastic CP because of its advantages of quick spasmolysis, strong selectivity, and fewer adverse effects.

BTX-A has a limited duration of action of approximately five months for the relaxation of spasticity. After BTX-A is administered, there is an obvious short-term improvement in the motor functions of children with CP. Maintaining long-term efficacy of BTX-A for spastic CP is considered pivotal by rehabilitation workers and the child's parents.

Only few studies have reported the long-term effects of BTX-A in children with CP¹⁰. This study aimed to investigate the long-term effects of BTX-A on relaxation of spasticity in CP.

Patients and Methods

General Materials

This study was approved by the Ethics Committee of the China Rehabilitation Research Centre for experiments involving humans. The parents of participating children received written and verbal explanations of the study and its evaluation procedures. Before the children were allowed to participate, their parents signed a consent form.

A total of 52 children with spastic CP were treated with BTX-A in our hospital between June 2015 and December 2018, including 19 outpatients and 33 inpatients. There were 34 males and 18 females, with the mean age of 37.9 ± 4.1 months (range: 20-56 months).

Diagnosis and clinical classification of CP were based on the standards of the Executive Committee for the Definition of Cerebral Palsy¹¹. The inclusion criteria were: spastic diplegia, lower extremity spasm in triceps surae, and posterior tibial spasm with abnormal postures such as tiptoeing, strephenopodia, and knee bending. The exclusion criteria were: contracture in ankle joints, obvious myospasm in iliopsoas, hamstrings, and adductor, allergic diathesis, and epileptic seizure.

The 52 CP cases were classified into the trial group and the control group by clinic time by randomly assigning them odd or even numbers. The children assigned odd numbers were included in the trial group, and the ones assigned even numbers were in the control group. Children ($n=27$) in the control group always received more than two hours of physical therapy training, including family and hospital rehabilitation, per day for two years. The training items were identified by rehabilitation therapists in our hospital. Children ($n=25$) in the trial group received BTX-A injection on the basis of rehabilitation trainings.

Methods

BOTOX (Allergan Inc., USA), containing 100 IU of BTX-A in each vial, was used in this study. It was kept at $2-8^{\circ}\text{C}$ or below -5°C . Prior to its use, it was diluted to 50 IU/ml solution with normal saline (NS). After preparation, the solution was stored at $2-8^{\circ}\text{C}$ for use within four hours.

The sterile injecting equipment included disposable insulation needles for nerve block (Japan), conductive paste, surface electrodes, and guidelines. G6805-2A therapeutic apparatus (Shanghai Huayi Electronic Instruments Plant) was used as the stimulator, with continuous wave, impulse frequency 2.667-83.333 Hz, current intensity 0-15 mA, and voltage 6 V.

The muscles involved in the BTX-A block were determined at the projection zone of the body surface based on their anatomical positions. The anode of a stimulator was fastened on the contralateral antagonistic muscle surface with adhesive plasters. The impulse frequency was set at 3 Hz, and the current intensity was set at 10-15 mA temporarily. After that, a proper position was repeatedly identified near the projection zone

with the cathode of the stimulator. Then, the position, marked with gentian violet, was determined as a block point where the corresponding muscle was maximally contracted at a minimum stimulating current.

The current intensity for the stimulator was adjusted to 3 mA under a constant impulse frequency. The skin to be treated was routinely disinfected. The insulating needle was connected with the stimulator cathode. The needle was inserted into the subcutaneous tissue at the marking point, and the inserting depth of the needle and the current intensity were adjusted. BTX-A was injected till the minimum current caused maximum contraction of muscles.

The triceps surae muscles (gastrocnemius and soleus muscles) were selected for homogeneity in this study. The tibialis posterior injection was administered to eight cases experiencing tiptoeing with strephenopodia.

The doses of BTX-A were selected based on the muscle spasticity (muscular tone) and the weight of the children. There were 4-6 injecting points for triceps surae muscles (gastrocnemius and soleus muscles). BTX-A was injected on each side at a dose of 45-150 IU, with an average 68.0 ± 31.6 IU at a time. The tibialis posterior injection was applied at 1-2 injecting points for eight children, and BTX-A was injected on each side at a dose of 20-70 IU, with an average 45.8 ± 18.3 IU at a time. No child underwent re-injection; they all received only one injection.

Evaluation

Before the nerve block, both muscle tone and motor functions of all children were evaluated. After operation, the children were evaluated every week until the modified Ashworth scale (MAS) reached the preoperative level indicating the termination of BTX-A acting time¹². The information associated with concomitant medication use was recorded. There were no concomitant medications used during the study.

Before the injection, the muscle tone and motor functions of the children were evaluated. The spasticity was measured using the MAS, and the motor function was determined using the Physician Rating Scale (PRS) and the gross motor function measure (GMFM). After two years of rehabilitation, all children were re-evaluated.

Statistical Analysis

The data are expressed as $(\bar{x} \pm s)$. The SPSS 13.0 statistical software (Chicago, IL, USA) was used for analysis. One Sample Kolmogorov-Smirnov

Table I. Comparison of general conditions of the trial and control groups.

Item		Trial group (n = 25)	Control group (n = 27)	X ² or T	p
Gender (n)	Male	17	17	0.146	0.703
	Female	8	10		
GMFCS (n)	I	12	11	0.277	0.598
	II	13	16		
Age (month)		37.2 ± 3.7	38.1 ± 4.1	1.086	0.318
Weight (kg)		14.1 ± 2.83	15.7 ± 3.15	1.218	0.257
MAS		2.18 ± 0.83	2.23 ± 0.96	1.127	0.298

test was applied for the normality test, and all data followed the normal distribution ($p > 0.05$). The *t*-test of paired samples was adopted for intra-group comparison, and the *t*-test of independent samples was applied for comparison among groups. The significance level was set at $\alpha = 0.05$.

Results

Comparison of General Conditions of the Children Between the Two Groups

The CP conditions were rated according to the gross motor function classification system (GMFCS); 23 cases were identified at GMFCS II and 29 at GMFCS III. The spasticity was measured using the MAS, which was converted into the following points: 1 point for MAS 1, 2 for MAS 1+, 3 for MAS 2, 4 for MAS 3, and 5 for MAS 4. No significant difference was observed with respect to gender, age, body weight, and MAS ($p > 0.05$) between the two groups, as shown in Table I.

Comparison of PRS Evaluation Between the Two Groups of Children

The onset time for the children was between 12 hours and 7 days after BTX-A injection (average 3.27 ± 1.87 days). The duration of the curative effect was between 9 and 33 weeks (average 19.38 ± 9.12 weeks). The diagnosing time was between 24 and 25 months after rehabilitation.

The comparison of PRS evaluation for the two groups of children is shown in Table II.

Comparison of Evaluative Dimension D in the GMFM Between the Two Groups of Children

The comparison of evaluative dimension D in the GMFM for the two groups of children is shown in Table III.

Comparison of Evaluative Dimension E in the GMFM Between the Two Groups of Children

The comparison of evaluative dimension E in the GMFM for the two groups of children is shown in Table IV.

Side Effects or Adverse Events

Side effects or adverse events associated with BTX-A administration in the children were recorded. A child experienced weakness for about four days after BTX-A injection, which was resolved in a week.

Discussion

The mechanism of spasticity is complex. It is generally recognized that spasms are caused by an extremely strong or sensitive spinal stretch reflex when a central lesion leads to improper

Table II. Comparison of PRS evaluation between the two groups of children.

Group	N	PRS prior to treatment ($\bar{x} \pm s$)	PRS after two years ($\bar{x} \pm s$)	T	p
Trial	25	7.05 ± 1.12	11.65 ± 1.52	2.697	0.011
Control	27	6.92 ± 1.05	9.01 ± 1.33		
T		1.674	2.372		
p		0.104	0.025		

T stands for T-value of the *t*-test, *p* stands for *p*-value.

Table III. Comparison of evaluative dimension D in the GMFM between the two groups of children.

Group	N	D prior to block ($\bar{x} \pm s$)	D after 2 years ($\bar{x} \pm s$)	T	p
Trial	25	29.06 \pm 3.01	36.25 \pm 3.86	2.531	0.016
Control	27	28.47 \pm 2.94	33.18 \pm 3.29	2.318	0.035
T		1.171	2.091		
p		0.267	0.042		

Dimension D stands for the function of standing and walking.

or abnormal control of the high central nervous system to a reflex. Spasticity is an important factor that leads to sluggish motor development and abnormal postures, including contractures, in children with CP¹³. However, it should be noted that the spasticity caused by CP does not occur in all muscles. Some muscles have a higher tone than others. In the calves, for instance, most children have a high triceps surae tone, but no spasm occurred in the tibialis anterior muscle leading to tiptoeing. The tiptoeing can be corrected by alleviating the triceps surae spasm.

Botulinum Toxin (BTX), a *Clostridium botulinum* of *Clostridium Praxmowski*, can produce strong exotoxin in an anaerobic environment. Based on the differences in toxin antigenicity, BTX-A can be divided into eight types: A, B, C1, C2, D, E, F, and G. As BTX-A is crystallized easily in the standard state, it should be diluted to 50 IU/ml solution with NS before use. For this reason, there are several studies on BTX-A. BTX is composed of a single polypeptide chain, is activated by proteolysis in the selective position, and is split into two segments. Its heavy chain has a molecular weight of 100,000 and the light chain has molecular weight of 50,000. First, the carboxyl end of the heavy chain is combined with the presynaptic receptor of cholinergic nerve endings, and its amino terminal forms the region for the channel. Subsequently, the light chain relocates into the cell to inhibit the quantum release of acetylcholine vesicles through an enzymatic

effect. Finally, the muscle contraction is weakened, and the muscle tone is reduced. After several months, the motor nerves control the muscles again by germination¹⁴.

Some studies¹⁵⁻¹⁸ have shown that BTX-A can significantly reduce muscle tone and can increase the motion of the joints when injected into the triceps surae muscle. After injection, it can improve the walking state and enhance the exercise performance^{19,20}.

In this study, there were no significant differences in the age and weight of the children in the two groups, indicating the homogeneity of the general conditions of these children. No significant differences were observed in preoperative GMFCS, MAS, and GMFM measurements, indicating comparable spasticity and motor functions. On this basis, the two groups of children were compared to completely eliminate any confusing factors and to ensure reliable results.

The BTX-A block improves the relaxation of spasticity but worsens contracture of muscles. The children with CP in this study suffered from triceps surae spasticity rather than contracture of the Achilles tendon. If the contracture should occur, the series plaster immobilization should be used to increase the motion of joints after the BTX-A block. This ensures that a higher efficacy is achieved²¹⁻²³.

Several factors influence the motor development of infants. These influencing factors co-determine the pattern and results of motor devel-

Table IV. Comparison of evaluative dimension E in the GMFM between the two groups of children.

Group	N	E prior to block ($\bar{x} \pm s$)	E after 2 years ($\bar{x} \pm s$)	T	p
Trial	25	32.05 \pm 3.63	53.47 \pm 5.27	2.984	0.004
Control	27	29.89 \pm 3.02	42.34 \pm 4.18	2.318	0.028
T		1.674	2.488		
p		0.119	0.019		

Dimension E stands for the function of running and jumping.

opment. Spasticity can hinder the motor development of children with CP, therefore leading to an abnormal motor pattern. The BTX-A nerve block maintains a curative effect for approximately 5-6 months. This treatment provides the children enough time for rehabilitation training due to relaxation of the spasticity. Children can receive rehabilitation training after relaxation of the spasticity and learn correct postures and movements. Through this, the right motor pattern is developed in their brains, and their big motions are developed^{24,25}. As a result, even if the BTX-A curative effect disappears after 5-6 months, the children have no declining motor ability, because they have learned the right motor pattern.

This study further confirms the above interpretations. Children in the trial group restored triceps surae spasticity to the preoperative level after receiving the BTX-A block for two years. However, the GMFM increased by some extent compared to that before the block; the GMFM of children in the trial group was significantly greater than that of the control group. This study shows the long-term efficacy of BTX-A on spastic CP.

This study had some limitations, including a lack of gait analysis. Furthermore, the study included children with diplegic CP only. To confirm similar observations in children with quadriplegic and hemiplegic CP, larger randomized trials including children with different types of spastic CP are needed.

Conclusions

This study showed that the BTX-A nerve block had a long-term positive effect. The rehabilitation training after the nerve block could help children to improve their motor functions.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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