Efficacy and safety of serial injections of botulinum toxin A in children with spastic cerebral palsy

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Original article

Background: **Botulinum toxin A (BTX-A) has been successfully used as a treatment for children with spastic cerebral palsy; however, the effect of BTX-A on reducing spasticity only lasts a few months, thus serial injections are required. The present study was to evaluate the efficacy and safety of serial injections of BTX-A in children with spastic cerebral palsy.**

Methods: **Fifty-two pediatric patients with spastic cerebral palsy, 2-12 years of age (mean age, 4.79±2.70), were retrospectively analyzed. Muscle tone was assessed with the Modified Ashworth Scale, and gait was assessed with the Physician Rating Scale. Assessments were undertaken at baseline, 3 months, and 6 months after serial injections of BTX-A.**

Results: **The beneficial effects of BTX-A occurred 1 week after the injection, whereas the adverse side-effects appeared within 1 week and lasted <2 weeks. BTX-A significantly improved muscle tone and gait 3 and 6 months after its serial injections compared to baseline (*P* <0.05).**

Conclusions: **Serial injections of BTX-A are effective and safe for children with spastic cerebral palsy. The side-effects of serial injections of BTX-A are mild and self-limited.**

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Key words: **botulinum toxin A;**
cerebral palsy;
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Introduction

Cerebral palsy (CP) is amongst a group of disorders characterized by the early onset and aberration in the control of movement without a recognized underlying progressive disease. CP is considered to be the main disease related to the impairment of motor function in children. Spastic cerebral palsy (SCP) is the most common type of CP, and accounts for 88% of patients. Spasticity is a clinical syndrome caused by upper motor neuron lesions, leading to a range of disorders in movement and postures, such as equinus foot, claspknife phenomenon, exaggerated tendon reflexes, clonus, and synkinetic movements.[1,2]

Botulinum toxin A (BTX-A) was first used for the treatment of CP in 1993.[3] In recent years, BTX-A has become an increasing treatment option for children with SCP. This potentially lethal neurotoxin exerts its main effect by blocking the release of acetylcholine into the presynaptic cleft at the presynaptic cholinergic nerve endings,[4-7] exerting a local denervating effect on spastic muscles leading to a functional benefit for the patient. On the other hand, the injected muscles are paralyzed until nerve sprouting establishes new junctions.[8,9] The regression of the neurite sprouts and the resumption of exocytosis from the previously BTX-A-intoxicated nerve terminals will then restore the neuromuscular junction to its original state.[10] To date, few studies have been published regarding the efficacy and safety of serial injections of BTX-A for Chinese children with SCP. In the current work, we addressed this issue retrospectively.

Methods

We retrospectively analyzed 52 pediatric patients with lower extremity SCP between January 2006 and January 2011. The spastic degree of muscles was evaluated according to the Modified Ashworth Scale of Spasticity (MAS) with 6 grades.[11] Informed consent forms for BTX-A injection were signed by parents or guardians. The study was approved by the Ethics Committee of Tiantan Hospital of the Capital Medical University and

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conducted according to the principles of *the Helsinki Declaration*.

Inclusion criteria

Children with SCP who were included in the study had clinical symptoms that improved shortly after the first BTX-A injection and muscle tone was >2 scores 6 months later, those who received one BTX-A injection, and those in whom BTX-A had no efficacy.

Exclusion criteria

Patients with fixed muscle contractures and a MAS score <2 were excluded. Also excluded from the study were patients who received other anti-spasticity treatments within 1 year and those who had acute infectious diseases, disorders of neuromuscular transmission, serious heart diseases, serious liver dysfunction, bleeding, or coagulation disorders.

Target muscles

Gastrocnemius, soleus, posterior tibial, and adductor muscles were chosen as target muscles. The gait was evaluated with the Physician Rating Scale (PRS), which includes 6 parameters (gait pattern, ankle position, hindfoot position during foot strike, knee position, degree of crouch, and speed of gait).[12]

Local intramuscular injection of BTX-A

An electromyogram was used to locate target muscles. The same muscles were repeatedly injected under sterile conditions. One hundred units of BTX-A were diluted in 5 mL of 0.9% sodium chloride in BTX-A vials to a concentration of 2.0 U/0.1 mL, according to the manufacturer's instructions. The dose of BTX-A administrated depended on body weight and the size of the spastic muscles; specifically 1-2 U/kg of BTX-A was used for the posterior tibial muscle; 2-3 U/kg of BTX-A was used for the soleus muscle; and 3-6 U/kg of BTX-A was used for the gastrocnemius, great adductor, long adductor, adductor, and hamstring muscles. Three-to-ten injections were administered at different sites in each target muscle at intervals of 5-10 mm. The maximum dosage was 10 U BTX-A per target muscle and 300 U BTX-A per patient. A 1-mL syringe with a 5-mL pinhead was used to control the injection velocity. The effects, side effects, and vital signs were recorded after each injection.

Evaluation

All subjects were evaluated at baseline. Following the injection, the patients were asked to stay in the hospital for approximately 10 days during which the effects and any side effects of the BTX-A injection were noted. The patients were followed up by telephone or surface mail after discharge from the hospital regarding the effects and side effects. The patients were evaluated in our outpatient department 3 and 6 months after the injections of BTX-A. Only one patient was excluded from the study due to a lack of effect with serial injections.

Statistical analysis

The MAS and PRS scores at baseline, and 3 and 6 months after injections were analyzed using a paired-samples *t*-test. The normality of distribution was examined using the Kolmogorov-Smirnov test. A P value <0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS 11.5 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

The present study included 52 children with SCP, the clinical data are presented in Table 1.

Repeated injections of BTX-A had an effect in 48 patients (92%) within 1 week, in 3 patients (6%) within 24 hours, and had no effect in one patient (a male, 4 years of age, who received 80 U of BTX-A) who was excluded from the study after 3 months. The effects of serial injections lasted various lengths of time, with 2 months in 4 patients (8%), 4-6 months in 42 (81%), and 6-8 months in 5 (10%). MAS and PRS scores revealed that there was a significant improvement in muscle

Table 1. Clinical data of the patients at baseline

Variables	Values
Mean age (SD), range	4.79 (2.70) y, 2-12y
Gender	
Male	36 (69%)
Female	16 (31%)
Classification of SCP	
Hemiplegia	12 (23%)
Diplegia	26 (50%)
Quadriplegia	10 (19%)
Triplegia	2 (4%)
Monoplegia	2 (4%)
Birth	
BW, mean (SD), range	2293 (704) g, 1100-4200 g
LBW	43 (83%)
GA, mean (SD), range	31 (3.93) wk, 24-39 wk
SGA	40 (77%)
Seizure	7 (13%): 5 cases with SPS, 2 cases with GTCS
Mental impairment	35 (67%)
Language impairment	14 (27%)

BW: birth weight; LBW: low birth weight (BW<3000g); GA: gestational age; SGA: small for gestational age; SPS: simple partial seizure; GTCS: generalized tonic-clonic seizure; SCP: spastic cerebral palsy; SD: standard deviation.

Table 2. MAS and PRS at baseline, 3 months, and 6 months after serial BTX-A injections

	Baseline	3 mon	6 mon
MAS*	3.10±0.66	1.60±0.63	1.93±0.61
		t=19.312, P<0.05	t=18.181, P<0.05
PRS*	6.33±2.83	8.58±3.17	9.50±2.87
		t=15.247, P<0.05	t=15.76, P<0.05

*: values are described as mean±standard error. 3 mon: 3 months after repeat injection; 6 mon: 6 months after repeat injection; MAS: Modified Ashworth Scaled Score; PRS: Physical Rating Scaled Score.

tone and gait 3 and 6 months after serial injections of BTX-A compared to baseline (Table 2).

Serial injections of BTX-A exhibited adverse side-effects in 6 patients (12%), which occurred most often within 1 week after the BTX-A injection and persisted < 2 weeks. The BTX-A-elicited adverse side-effects were local, mild, and self-limited, and manifested as local weakness (4 patients, 8%) and local pain (2 patients, 4%). No severe or systemic reactions were observed in the present study.

Discussion

BTX-A injections have become increasingly popular for the treatment of children with SCP, which benefits patients by relief of muscle spasticity and an increase in the extent of joint movement. The efficacy and safety of BTX-A in children with SCP have been validated in randomized controlled trials.[3-7] Histologic studies have shown no evidence for the persistent changes in nerve terminals or target muscles following BTX-A administration.[1,13,14] New nervous endplate units have been shown to regenerate within several months of treatment with BTX-A. Consequently, the muscle chemoparalysis caused by BTX-A, as well as the effect of BTX-A, is transient. The long-term effect of BTX-A treatment in children with CP is still elusive. A recent study involving the upper extremities of children with CP showed that the mean duration of the effect of BTX-A injection was 7.0±3.0 months.[15] In the present study, the reduction in spasticity after BTX-A administration occurred within 1 week, and the clinical effect lasted 2-8 months. A number of variables, such as the dose of BTX-A, target muscles, patient age, and BTX-A formulations, may contribute to this difference, as some studies have suggested.[15-17]

The joint crouch, a movement involving the hips, knees, and ankles, was markedly improved after BTX-A treatment in the current study. This improvement may be attributable to the following reasons. Firstly, spasticity of the gastrocnemius is a major factor that interferes with normal walking by preventing heel strike. Serial injections of BTX-A into the gastrocnemius, soleus, and posterior tibial muscles favor a reduction in spasticity of these muscles, thus promoting the formation of a normal heel-toe gait. Secondly, spasticity of the gastrocnemius and soleus muscles is superficial and easy to locate in a contractive state. Thirdly, malformation of the hip and knee joints is usually secondary to the toe-toe walk, and the flexibility of the joint crouch will be ameliorated if the toe-walk is improved. However, once malformation of the joint develops into structure fixation, serial injections of BTX-A are likely to be ineffective.

BTX-A injection into hip adductors can improve sitting and a scissoring gait, especially for severe patients with SCP. To attain an optimal effect, BTX-A injections should be repeated once or twice per year because serial injections before the peak of the BTX-A effect are reported to promote a further decrease in muscle spasticity.[18-26]

No serious adverse events were observed in the current study, and the side-effects were local, mild, and self-limited,[27,28] suggesting that serial BTX-A injections are tolerable for children with SCP. Only one patient (2%) did not achieve a favorable response to serial BTX-A injections in the current study; the incidence of secondary failure was in agreement with previous reports. Secondary failure may be due to the formation of BTX-A antibodies; indeed, high doses of BTX-A have been reported to induce BTX-A antibody production.[29,30] Nevertheless, some studies have suggested that BTX-B might be effective for patients with secondary failure of BTX-A.[31-34]

In summary, the results from the present study have shown that serial injections of BTX-A is an effective and safe treatment for children with SCP, and able to decrease the tone of involved muscles. However, this was a retrospective study, and the dosage, effect, and safety of serial injections of BTX-A for children with SCP need further validation in large samples of prospective case-control studies.

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