

Effects of botulinum toxin injections to the iliopsoas combined with physical therapy on gross motor functions in cerebral palsy.

Ying Wu¹, Qiu Luo¹, Mei Tang¹, Liqing Yao¹, Mai Li¹, Chunjun Zhang¹, Yongmei Li¹, Zhengcai Li^{2*}

¹Department of Rehabilitation Medicine Center, the Second Affiliated Hospital of Kunming Medical University, Kunming, PR China

²Department of Ear-Nose-Throat, Kunming Children's Hospital, Kunming, PR China

Abstract

The present study aimed to investigate the effects of botulinum toxin injections to the iliopsoas combined with physical therapy on gross motor functions in patients with cerebral palsy. This retrospective study consisted of 80 subjects diagnosed with cerebral palsy associated with diaphragma, who were randomly divided into two groups: the experimental group (n=40) and control group (n=40). Subjects in the experimental group were treated by physiotherapy along with injection of 48-100 U botulinum toxin type A (Botox, Allergan) in the neuromuscular junction of the iliopsoas, whereas subjects in the control group received physiotherapy alone. Gross motor changes were evaluated using Gross Motor Function Measurement Scale (GMFM), and muscle spasm was evaluated by the Ashworth Scale and hip joint angles before the treatment and 3 days, 7 days, 1 month, 2 months and 3 months post-treatment. Data were analysed using the one-way ANOVA test ($P<0.05$). The results demonstrated an increase in the scores of GMFM in both groups following intervention; however GMFM scores were significantly increased in the experimental group ($P<0.01$). Significantly increased hip angles and decreased iliopsoas muscle spasms were detected in the experimental group ($P<0.05$). In conclusion, the present study demonstrated that botulinum toxin type A injection to the iliopsoas muscle combined with physiotherapy was an efficient method of treatment for cerebral palsy patients with diaphragma.

Keywords: Cerebral palsy, Muscle spasm, Iliopsoas, Botulinum toxin.

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Introduction

Cerebral Palsy (CP) typically refers to a series of brain parenchymal lesions, which may affect actions, appearance, and development, thereby limiting human activity as well as causing non-infectious permanent pathogenic disorders occurring in fetal or infant brains [1]. Cerebral palsy is a common disabling adolescent disease [2]. Spastic cerebral palsy is a common type of cerebral palsy, accounting for ~80% of all cerebral palsy cases [3]; therefore, anticonvulsant therapy is a key issue in cerebral palsy rehabilitation. Botulinum toxin type A (BTXA) is a white loose product that has shown clinical efficacy in eye spasms and facial spasms treatment [4]. In recent years, BTXA has been used to treat spastic cerebral palsy in fetuses and infants [5]. BTXA, a protein product of *Clostridium botulinum*, is a potential agent of neuromuscular paralysis that can relax muscles, reduce muscle tension, and improve limb spasticity and abnormal muscle spastic posture; therefore, it may be suitable as a treatment for limb spasticity caused by significantly increased tension and abnormal posture control [6]. Owing to the difficulty in positioning with the iliopsoas due to its deep location, few previous studies have investigated iliopsoas BTXA treatment. However, it has been

demonstrated that iliopsoas spasticity can lead to abnormal hip flexion, abnormal posture, difficulty standing and walking, and the blockage of motor function development in fetuses and infants with cerebral palsy [7]. Passive range of motion training is a traditional way of reducing iliopsoas muscle tension. However, the results are often poor. Therefore, an approach to reduce iliopsoas muscle tension and improve walking ability in children is urgently required. The present study aimed to investigate whether combination therapy with rehabilitation and administration of BTXA injection into the iliopsoas could improve walking ability in children with cerebral palsy and diaphragma.

Materials and Methods

Inclusion and exclusion criteria

The present retrospective study consisted of 80 cerebral palsy subjects of both sexes, with bilateral iliopsoas muscles spasm. Patients were recruited from the Department of Rehabilitation Medicine at the Second Affiliated Hospital of Kunming Medical University in China during the years of 1999-2007 and were included in the study if they met the following

criteria: (1) medical diagnosis of diaphragm and cerebral palsy and (2) unilateral or bilateral lower leg muscle spasticity. Potential patients were excluded because of general (hypersensitivity to BTXA, Eaton-Lambert syndrome, and treatment with aminoglycosides or curare-like compounds) and/or local (infection at the proposed site of injection) contraindications for intramuscular BTXA injections, or the absence of consent to be involved in the study. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the Second Affiliated Hospital of Kunming Medical University. All subjects with their parents in both groups were voluntarily joined this study with informed consents.

Botulinum toxin injections

Injected muscles included the bilateral iliopsoas, hamstring muscles, triceps surae, and adductor muscles. Unilateral iliopsoas dosage was determined according to the degree of spasm (MAS). According to Liu et al. [8], BTX-A ideal unit dose and preoperative MAS score, our choice of botulinum toxin dose is mainly based on the calculation of MAS score. There is a linear positive correlation BTX-A ideal dose calculation formula: dose (IU)=(MAS score+2.5) × body weight (kg), we use this formula to calculate the dose of unilateral iliopsoas.

A mean dose of 48 U and a maximum dose of 100 μ BTXA were injected into the unilateral iliopsoas on two separate days to determine the appropriate dosage. Botulinum toxin (100-110 μ) was purchased from Lanzhou Biological Products (Lanzhou, China); 2 ml BTXA was subsequently diluted in 0.9% saline, in strict accordance with the method of the dilute solution (concentration, 50-55 μ/ml; 0.2 per 10 μ/ml). The electrical stimulator-guided injection to the iliopsoas muscle was performed using an electrical evoked potential instrument (Allergan Company), with a disposable nerve block insulation needle (referred to as insulated needle). The needle inside and outside the surface is of the insulating material Teflon (Teflon, Polytetrafluoroethylene), only the tip of the slope is bare. The needle body is connected with a wire and a syringe, and the other end of the wire is connected with a conductive small clip. The other end of the injection catheter can connect the syringe of the syringe. So that when the insulation needle into the body, only the tip part is conductive. Remove the insulated needle with the help of the assistant, and the needle body remains sterile. The assistant clamps the small clip of the insulated needle wire on the electrical stimulator and connects the injection catheter of the insulated needle to the syringe of 1 ml syringe. The current intensity of the stimulator from 0.5 mA began to increase, the maximum current doesn't exceed 3 mA, until the emergence of muscle contraction (flexion and hip movements) so far, you can inject drugs by the assistant. 1) Injection to the iliopsoas muscle along the iliac spine was performed as previously described [9]. With the patient in a supine position and bent at the knee to expose the hip flexor muscle tension, the needle was inserted in front of the iliac spine on the medial side and was opened 1 cm and tipped 5 degrees to the iliac crest of the needle, until the emergence of

muscle contraction without drawing blood into iliacus injection. The needle tip was changed and subsequently inserted into the ilium, (tilted 45 degrees laterally to the ilium) to until the emergence of muscle contraction, without drawing blood. For the waist muscle injection, 2) iliopsoas muscle injection was performed as follows [9]: With the patient in a supine position with their legs and hip flexed with knees outwardly turned and an assistant to hold their knee, hamstring root and hip flexion muscle tension was exposed. The needle was inserted along the margin of the medial rectus muscle in order to until the emergence of muscle contraction, after withdrawing blood via injection. The principle states that every 1-3 cm² per 1 point is one spasm of the muscle. The surface of the skin should not be scrubbed nor should the muscles be massaged within 6 h after injection.

Physiotherapy training

The experimental and control groups simultaneously received antispasmodic muscle rehabilitation therapy following BTXA injection. The control group and the experimental group were a month of PT treatment. During physiotherapy, subjects assumed a continuous prone position in order to stretch the iliopsoas, hamstring, and gluteus muscles, and to perform muscle strengthen training, kneeling and standing function training, and partial weight support training.

Clinical assessment

Gross motor changes were evaluated using the Gross Motor Function Measurement Scale (GMFM), and muscle spasm was evaluated by the Ashworth Scale and hip joint angles prior to the treatment and 3 days, 7 days, 1 month, 2 months and 3 months post-treatment. All responses from parents were recorded.

Statistical analysis

Data were analysed using the one way ANOVA test, with statistical significance at $P < 0.005$. SPSS 11.5 software was used for all statistical analyses.

Results

Joint range of motion and modified Ashworth scale changes

The experimental group exhibited significantly improved hip extension range of motion and iliopsoas modified Ashworth scores after treatment for 3 days, 7 days, 1 month, 2 months and 3 months, as compared with the respective values prior to treatment ($P < 0.01$). The most significant effect was demonstrated 1 month post-treatment ($P < 0.001$). In the control group, no significant improvement in hip extension and iliopsoas modified Ashworth rating was detected 3 days or 7 days post-treatment, as compared with before treatment ($P > 0.05$). However, 1 month, 2 months and 3 months later, these scores changed significantly ($P < 0.05$), as compared with prior to treatment. Therefore, both groups exhibited a

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significant difference in hip extension and iliopsoas modified Ashworth scales scores ($P < 0.01$); however, the experimental

group exhibited a marked improvement; as compared with the control group (Table 1).

Table 1. Compare two groups difference in hip extension, MAS for Iliopsoas and GMFM scores ($\bar{x} \pm s$).

Items	Group	Before treatment	After treatment 3 days	After treatment 1 month	After treatment 1 month	After treatment 2 month	After treatment 3 month
Hip extension	Experimental	-10.80 \pm 3.916	-6.80 \pm 3.652 [*]	-5.83 \pm 3.514 [*]	2.37 \pm 3.605 [*]	1.77 \pm 3.298 [*]	-0.47 \pm 3.350 [*]
	Control	-10.75 \pm 3.872	-10.51 \pm 3.820	-10.13 \pm 3.233	-7.36 \pm 3.142 [#]	-5.26 \pm 3.220 [#]	-3.45 \pm 3.131 [#]
Iliopsoas MAS scores	Experimental	3.75 \pm 0.676	3.21 \pm 0.779 [*]	2.71 \pm 0.690 [*]	2.27 \pm 0.550 [*]	2.63 \pm 0.684 [*]	2.86 \pm 0.684 [*]
	Control	3.68 \pm 0.626	3.66 \pm 0.535	3.63 \pm 0.612	3.06 \pm 0.616 [#]	2.95 \pm 0.584 [#]	2.90 \pm 0.621 [#]
GMFM scores	Experimental	73.37 \pm 13.158			83.83 \pm 13.499 [*]	88.30 \pm 13.256 [*]	92.97 \pm 14.063 [*]
	Control	72.28 \pm 13.410			78.48 \pm 13.882 [#]	83.46 \pm 13.116 [#]	88.87 \pm 12.878 [#]

^{*} $P < 0.01$, compare difference within experimental group; [#] $P < 0.05$, compare difference within control group; $P < 0.01$ compare two groups after treatment.

Gross motor changes (GMFM)

Increased GMFM scores, associated with crawling, kneeling, standing and walking, were demonstrated after 1 month, 2 months and 3 months of treatment in both groups; however, the experimental group exhibited significantly increased scores, as compared with the control group ($P < 0.01$).

Correlation analysis

Hip extension range of motion and iliopsoas muscle injection dosage exhibited a significantly negative correlation ($r = -0.793$, $P < 0.01$) prior to treatment, whereas the iliopsoas modified Ashworth scale and iliopsoas muscle injection dosage demonstrated a significantly positive correlation ($r = 0.698$, $P < 0.01$).

Complications

Among 40 cases of control group, four cases had side effects, one case of postoperative wriggling, one case of rash, one case of sensory symptom, one case of pain at injection point. Among 40 cases of treatment group, three cases of side effects, one case of rash, one case of sensory symptoms, one case of injection point pain. We did no special treatment only depending on the self-mitigation. Because of the fact that the number of side effects occurred less, there is no statistically significant.

Discussion

Spasm cerebral palsy is the most common type of cerebral palsy; 80% of children with cerebral palsy will exhibit spasticity, which limits childhood activities and daily life [10]. In addition to cramping, which is associated with acute pain, long-term spasm can induce muscle contracture, hip dislocation, and scoliosis [11-14]. All subjects enrolled in the present study exhibited diaphragma cerebral palsy with the following similar characteristics: 1) motor dysfunctions in prone crawl, kneeling on knees and kneeling on four points, legs crossed in standing or walking position, hip internal

rotation, hip and knee flexion, ankle in dorsiflexion or inversion; 2) abnormal posture control, knee and hip flexion posture in the supine position, lower limbs into the "W" shape in kneeling position, hips and knees slightly bent when standing, and scissor-like gait. When standing up to walk with two legs, the cross position is assumed with knee flexion contracture, hip flexion, adduction, and internal rotation. Therefore, the iliopsoas is very important for lower limb functions.

The treatment strategy for muscle spasticity is predominantly physical therapy, and gradually decreased muscle spasm is typically observed two weeks after treatment; however, the treatment effect is limited to a clinical setting. Botulinum toxin can be produced from *Clostridium botulinum* in order to decrease the strong virulence of the bacterial toxin, usually in a nerve poison and hemagglutinin complex form; therefore, it can be applied to motor nerve endings neuromuscular junction to inhibit presynaptic membrane acetylcholine release and induce muscle relaxation. It has been demonstrated that BTXA is effective for local muscle spasm and segmental spasm [15-17], and studies have found that combination therapy with other physiotherapy methods, such as muscle strengthening exercises, has more effect than a single injection of BTXA [18]. In recent years, several studies have demonstrated that spastic muscle injection of BTXA with joint rehabilitation has a good clinical effect on spastic cerebral palsy in children, effectively relieving the spasm and improving gross motor function, thus enhancing the therapeutic effect [7,19-25]. Due to the iliopsoas muscle position is deep, the BTXA injection has a certain degree of difficulty of conducting, and there are few previous studies. Under the guidance of the electrical stimulation of the body with the muscle surface orientation, we did better cerebral palsy in children with iliopsoas muscle BTXA injection, which can effectively improve the children's motor function.

The present study was designed to investigate BTXA injections to the iliopsoas in combination with physical therapy for the rehabilitation of walking ability in children with cerebral palsy and diaphragma. The results indicated that combination therapy

with BTXA injections to the iliopsoas and physical rehabilitation can effectively increase the hip extension angle, reduce iliopsoas muscle tension, and improve walking ability, which is consistent with our hypothesis. In the present study, two groups of children with cerebral palsy were assessed for gross motor function, among these 88 items, scores associated with climbing, kneeling, standing and walking ability exhibited a statistically significant difference ($P < 0.01$) prior to and following treatment. Similar significant differences were detected between the treatment and control groups, and within the treatment group, the climbing, kneeling, standing, and walking abilities significantly improved. These results are consistent with previous findings [7].

In the treatment group, the hip extension angles and iliopsoas modified Ashworth grades significantly improved after treatment for 3 days and 7 days ($P < 0.01$), which demonstrated that considerable improvement was detected before the treatment duration was sustained. Notably, the treatment effect after 1 month was the most significant ($P < 0.001$). In the control group, no improvement in hip extension angle or iliopsoas Modified Ashworth grade was detected after treatment for 3 days and 7 days, and no significant difference was demonstrated before and after treatment ($P > 0.05$). The therapeutic effects on hip extension angle and iliopsoas modified Ashworth grade exhibited by the treatment group after treatment for 3 days, 7 days, 1 month, 2 months and 3 months were improved, as compared with the control group. These results demonstrated that botulinum toxin injection in the early treatment period can effectively reduce iliopsoas muscle tension, which expedites rehabilitation and improves long-term treatment.

The present study showed that muscle spasm reduced one week after injection with BTXA, and the duration of this effect was 2-8 months. Influencing factors included the efficacy of botulinum toxin, size of the target muscles, patient age, and the dosage of botox, all of which could lead to a varied effect [26-28]. Previous studies have found that in order to achieve an optimal curative effect, BTXA injections should be repeated once or twice per year, to achieve the maximum effect and attain long-term curative solution [29-37]. To date, no significant side effects of BTXA have been observed, as any side effects have been local, mild and self-limiting [38,39], which suggests that the injection of BTXA is suitable for children with cerebral palsy.

In the present study, the duration of botulinum toxin onset was 48-72 hours; this quick response will enable therapists and patients to achieve the goal of releasing muscle tone. Treatment technology is a key to determining the target muscle due to the deep location of the iliopsoas. However, Electrical Stimulation may be used to locate the iliopsoas, allowing clinicians to accurately inject into the muscle and ensure accuracy. Previous studies have shown that Electrical Stimulation-guided injection of botulinum toxin can improve the target accuracy of intramuscular injection, as compared with hand injection [40].

Botulinum toxin-induced spasm inhibition is a reversible process. The majority of subjects exhibited decreased muscle tone 48-72 h post-injection, with the maximum effect lasting one month after injection. However, the most important factor to consider is the GMFM score, which demonstrated continuous functional improvement. A few children exhibited adverse effects such as drowsiness, anorexia, and fever; however, the duration of these symptoms was only 2-3 days. Finally, the botox injections were combined with physiotherapy following BTXA injection; therefore, the two methods function synergistically to obtain the maximum therapeutic effect for patients.

In conclusion, BTXA injections for children with cerebral palsy may be an effective and safe treatment method. However, as this is a retrospective study, further prospective case-control studies are required in the future to determine the appropriate dosage of BTXA for iliopsoas muscle injections. There are still some limitations in our research. Although we use the electrical stimulation for the positioning, the iliopsoas muscle surface position is not significant, deep subtle muscle. Studies have shown that electrical stimulation guidance did not show complete accuracy when measured using ultrasonography [41]. So if it was combined with ultrasound-guided injection technology, we could more accurately locate the boundaries of the target muscles, and could be more intuitive to observe the location of the needle to control the depth of the needle. In the future, we plan to combine the electrical stimulation and ultrasound technology in this area.

Conflict of Interest

All authors have no conflict of interest regarding this paper.

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***Correspondence to**

Zhengcai Li

Department of Ear-Nose-Throat

Kunming Children's Hospital

PR China