Application of Botulinum Toxin Intramuscular Injection on Rehabilitation Training of Cerebral Palsy Children

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Abstract

Objective: To study the effects and side effects of botulinum toxin A (LANTOX) intramuscular injection on correcting the cerebral function deformity in cerebral palsy (CP) children and its significance in rehabilitation training.

Method: The dose of LANTOX injection to motor points of spastic muscles was 1 – 2IU/kg of body weight. No effects were presented after one month of initial injection; the injection dose must be increased repetitiously.

Result: Among 12 CP children with non-ambulatory or unstable ambulatory, 5 cases appeared stable gait and 5 cases were walking with support at two months after injection. In 7 cases with upper limb deformity, 3 cases were recovered and 3 cases improved and 3 cases improved. No relapse and side effects were found after 2 – 17 months of follows-up.

Conclusion: It is indicated that the LANTOX injection is a safe, effective and non-invasive therapy for spastic and athetotic CP children.

Key words: Rehabilitation; Cerebral palsy; Botulinum toxins

Among those children with cerebral palsy (CP) receiving rehabilitation training in 2nd June 1997 to 10th September 1998, 18 cases were treated with LANTOX to correct the muscular spastic deformity and there are different intensities in the satisfaction of the results. The analysis and conclusion are as follows.

Background and Method

Among the 18 cases, 12 are male and 6 are female; the ages are from 6 months to 24 years old; 9 cases are spastic, 9 are athetotic with spastic, 10 are abnormal gestation in mothers or with taking drugs background, 7 cases are premature delivery, 1 case is overdue delivery, 6 cases are abnormal labor, 7 cases are low birth weight, 9 cases are straitened breathing or icterus, according to the patients' qualities of development, at most 15/18 are little head deformity, 11/18 with IQ lower than 70 marks, 18/18 have achievement quotient behind of the affected limbs (ranged from 3 months old to 14 years old). 9 cases show abnormality after CT checking. Blood types of 8 child patients and their mothers are B, O or A, O. 1 child who has normal gestation period

and with smooth going labor has family history.

LANTOX (made in Lanzhou), should be stored in ice box at -5 to -20℃. It should be diluted with saline before injection according to your own need. 1 ml needle is used for injection, the dosage is the international unit, using ultra-micro level, which is equivalent to the ng dosage[1]. In general, the amount of dosage used is based on the weight (in kg) and the size and amount of the target muscle. 1 – 2 IU/kg is used according to the report made by Koman[2] and Sanchez[3]. However, 3 – 4 IU/kg is used when muscular spasm is serious or deformity is apparent. If no effect is observed or the effect is not satisfactory after the first injection, injection can be repeated within one month, but the dosage used should be greater with the maximum 6 IU/kg of weight.

Selection of target muscle: The target muscles are those spastic muscles that lead to deformity, for example, before the elbow is stretched or rotated, muscular triceps brachii, round prunator muscles and square pronator muscles are selected. In case of crossing legs and talipes, addactor muscles and muscular triceps brachii are selected. Orientation of injection: Motor point is found out by electrical excitation on superficial target muscles. When regular derma is disinfected, 2 – 4 points are injected around the dynamic point. Dynamic point can not be found in profound target muscle. In general, EMG is used to supervise the injection. In order to reduce the level of pain, EMG supervision is not used, but injection is carried out by professionals who are familiar with the EMG technique. In order to prevent disturbance on major blood vessel and nerves, the injection in the posterior border of tibia[4] is adopted for the profound target muscles.

Time of injection: Wong[5] requested to undergo the rehabilitation training and physiotherapy for 3 months, this kind of treatment is reasonable. During this period of time, primitive reflex is inhibited, posture response is induced, and coordinated balance is established. Although there are improvement in crossing legs and talipes deformity, child patients still can not stand or walk if the above abnormal appearances are not solved. Thus, rehabilitation training is still needed to allow the child patients to build up their own coordination when they move. This is especially essential for those child patients who do not have the concept of standing and walking. There is no time limitation of injection before child patients with upper limb deformity successfully build up their own body balance. This accomplish the capability to both limbs in advance, which is advantageous in obtaining food, toys, IQ development, social communication like waving his hands to say goodbye or to applaud.

Training of antagonistic muscle: After the start of rehabilitation training, attention should be paid on the training the antagonistic muscles of the spastic muscles to strengthen the antagonistic muscle. We normally use massage, acupuncture, electrical excitation and mechanical training.

Time of observation: there should be one subsequent consultation within 72 hours after LANTOX injection. If there is any significant effect, subsequent consultation should be made once a month. If there is not any observable effect within 72 hours, checking should be made after 1 week but not exceeding a month for the ease of re-injection. Effectiveness should be seen within 72 hours. Using Koman's Physician rating scale (PRS), with the combination of the characteristics of our cases, the standard of judgment is concluded in Table 1.

Table 1 Physician rating scale (PRS)

Elbow twist	**Score**	**Talipes**	**Score**	**Crossing leg thigh angle**	**Score**
Deformity fixed unchanged	0	Deformity fixed unchanged	0	<30°	0
Passive changeable deformity	1	Improved passive deformity	0	<40°	1
Deformity but occasionally back to normal	2	Heel touch floor occasionally	2	>60°	2
Free movement	3	Heel touch floor normally	3	>60°	3

Angles of both thighs being separated

(Children can not rationally separate their thighs)

Result

We observed 12 child patients who are old enough but still not capable to walk or walk stably. 8 cases can walk stably with improvement in gait after treatment. Case study 1: Spastic CP left talipes, cannot go to school at the age of 9 due to unstable walk. After injection of LANTOX with 2 months rehabilitation training, the child can walk stably and go to school. Case study 2: A girl who is 6 years old, spastic CP in both lower limbs, crawling with no choice. 3 months after LANTOX injection can walk into preschool. Case study 3 showed immediate effect: He had treatment outside but still can't walk when he is 3 years old. The next morning after LANTOX injection, he shouted suddenly, 'My calf is feeble, let me walk!' eventually he can walk with

occasion fall down. Finally he can walk stably on the third day and delivered from hospital after 1 week. For those who are not old enough to walk, training after LANTOX injection is focused on “foot on floor” standing and assisted walking. 7 child patients with upper limbs deformity (4 cases accompany with lower limps palsy) show improvement 1-2 weeks after LANTOX injection. 3 cases in restoration of deformity, 3 cases show improvement. Functional training of upper limbs need more time than those of lower limps.

We made comparison on before and after treatment of LANTOX in all 18 cases of CP. It can be seen from Table 2 that in all 14 cases of talipes deformity, 6 cases are cured completely. The four cases of crossing legs can reach normal thigh angle. 7 cases show elbow and twist deformity, 3 cases recovered, 3 cases are improved, and 1 case fail. TV recording is prepared for showing motional changes. No relapse and side effects were found after 2 – 17 months of follow-ups.

Table 2 CP child patients, PRS before and after LANTOX treatment

Case No.	Talipes				Crossing leg thigh angle		Elbow deformity			
	Before		After		Before	After	Before		After	
	L	R	L	R			L	R	L	R
1	1	1	3	3	0	3				
2	2	1	3	2						
3		1		2						
4	1		3							
5	1	1	2	3						
6	0	1	1	2						
7	1	1	3	3						
8	1	1	3	3	1	3				
9	1	1	3	3	0	3	2		3	
10	1	1	2	2			1	1	2	3
11	1	1	2	3			2	2	2	3
12							2	2	3	3
13	1	0	3	2						
14	2	2	3	3			2	2	3	3
16							2		2	
17								1		2
18	1	1	2	2	2	3				

Discussion

All damages from embryo development to childhood after birth which cause cerebral motion handicap and abnormal posture are regarded as cerebral palsy (CP). It usually accompanies with handicap in vision and hearing, difficulty in swallowing, non-fluent language and insignificant IQ. The fundamental treatment of CP is based on rehabilitation training. However, the deformity resulted from muscle spasm is a great obstacle in training. Oral taking drugs[6] have been used for a long time to improve muscle spasm, but the result is not satisfactory and there are side effects. In 60's alcohol and intramuscular neurolysis[7] were used. Under the condition of whole body anesthesia, pain at injection sites, derma gangrene and different level of sensing handicap were common. Surgery brought about complication of the respiratory tract, infection of wound and difficulty in caring of fixed gypsum. It is common that patients still couldn't stand and walk after surgery.

In recent 20 years, there was breakthrough in the research of neurotoxin. The fact is to

"turn menace to medicine"[8]. The major function of LANTOX is relaxing the spastic muscle. LANTOX was applied firstly by Scott[6] on the treatment of blepharospasm and strabismus. In 1992, Cosgrove was the first to apply LANTOX on clinical CP. In 1993, Koman[2] formally published the application of LANTOX on CP dynamic deformity (that is deformity turns back to normal position after forcing passively). Many scholars confirm the possibility of this treatment later on and this became the focus in medical science. Numerous journals were published. According to medical resource in internet and related literatures up to 10th November, 1998, there were totally 26 journals with 418 cases which discussed the application of LANTOX on clinical treatment of CP. Researches came from the United States of America, United Kingdom, Germany, France, Spain, Slovenia, South Africa, Israel, Japan and Hong Kong. All confirm the efficacy and safety of LANTOX on the treatment of CP with any damage.

Drug property and functions: In 1895, 34 members from a Belgium club suffered from muscular spasm with characteristics like neuroparalysis after eating pickled ham. Van Ermengem[11] isolated botulinum toxin from individuals and food, thus the disease is called "botulism". Afterwards, 8 types of botulinum toxin were found, which were A, B, C1, C2, D, E, F and G. All types are neurotoxins except C2 which is cytotoxin. Toxicity of LANTOX is the greatest, most stable, easy to prepare and can be stored under low temperature for a long time.

The botulinum toxin molecule is synthesized as a single chain then cleaved to form the dichain molecule. The light chain (50 KDa) acts as endopetidase, with proteolytic activity[12]. The heavy chain (100 kDa) provides cholingeric specificity and promotes light chain translocation across the endosomal membrane. After entering the muscles, LANTOX binds to the presynaptic membrane with high affinity. Thus toxin seldom enters the blood circulation or passes through the brain barrier. This is also the reason why it is not easy to trigger systematic or whole body toxic side effect. LANTOX functions at the presynaptic membrane to inhibit the release of acetylcholine, no nerve impulses are generated and thus muscular tension is reduced. The reduction or disappearance of dynamic electrical point of EMG is the strong evidence of the relaxation of spastic muscle[13,14]. Single-fiber EMG checking found that electrical increased occasionally, this further proved that relaxation of spastic muscle is caused by obstacle in nerve transmission to muscles[14]. However, LANTOX is not destructive to presynaptic membrane, when new nerves shoot out after 3 – 6 months, new end plate is formed to preserve its characteristics and muscular spasm can be happened again[13].

LANTOX injection is a essential auxiliary technique of rehabilitation training, LANTOX can relieve muscular spasm, to cure dynamic deformity caused by spastic muscle, thus creating advantageous conditions for CP rehabilitation training. Most reports claim LANTOX is effective for 3 – 6 months or 7 – 8 months. Arrangement of rehabilitation training is crucial in this limited time. For example, strengthening of antagonistic muscle and building up body balance response are crucial while these are far more important to child patients who do not have the concept of standing and walking. It is because the majority of these child patients show positive in the reflex of lateral camptocormia, thus this fundamental reflex should be inhibited in advance. If the fundamental reflex is not inhibited, posture response is not reduced, early injection of LANTOX can improve deformity but functional restoration may not be satisfactory. Russman[15] suggested that CP child patients who are younger than 18 months old should not be treated with LANTOX but without any explanation. We think that when the child patients can stand or walk with assistance, lower limps can be injected with LANTOX while earlier injection is beneficial for upper limps.

Immunology of LANTOX: LANTOX is effective for 3 – 6 months. So, it can be re-injected or not is the practical problem that needs to be solved. After LANTOX injection, our bodies can generate LANTOX antibody. This antibody neutralizes the re-injected LANTOX, which causes it fail to function. BTX-B and BTX-F could be used instead to obtain desired result[16]. This stated that each type of toxin had unique immunity without crossing response. Someone suggested[17] that when the memorizing immunity response fade out, or when the antibody of LANTOX changed from positive to negative, re-injection of LANTOX showed desired treatment result. The immuno-phenomenon is meaningful guideline for clinical research.

Usage of LANTOX and points to notice: Application of LANTOX on the treatment of CP is a new technology in recent years, but it is widely spread and applied. The efficacy, safety and non-destructive properties are confirmed. However, usage should be delayed when patients are having fever or they are taking aminoglycoside antibiotics (gentamycin, neolmycin, streptomycin, etc). Those who are suffering from neuromuscular transmission handicap such as serious myasthenia should avoid using LANTOX, particularly LANTOX is a highly toxic drug. The dosage used, target muscle selection, site of injection are strict followed. It is very dangerous to use it without proficient operating skill and a required physiological knowledge.

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