

Botulinum toxin type-A overdose for the treatment of spastic muscles in two patients with brain injuries.

Jiang Li^{1,2*}, Ru Zhang³, Xiaoyan Xu⁴, Xia Chen⁴, Guangtao Bai², Yifeng Du¹

¹Department of Neurology, Shandong Provincial Hospital to Shandong University, Jinan 250021, Shandong, PR China

²Department of Rehabilitation, the Affiliated Hospital of Qingdao University, Qingdao 266003, Shandong, PR China

³Department of Information Statistics, the Affiliated Hospital of Qingdao University, Qingdao 266003, Shandong, PR China

⁴Department of Stomatology, the Affiliated Hospital of Qingdao University, Qingdao 266003, Shandong, PR China

Abstract

Spasticity is commonly encountered clinically, and always affects patients' motor ability and capacity for self-care which necessitates intervention. At present, numerous methods have been proposed with varying effects. Many reports show that the most effective method is to inject botulinum toxin, type A (BTX-A) into the spasming muscles, but the doses are different. The guideline of BTX-A injection in Chinese adults is restricted to 600 IU each time within 3 months. In this article, we treated two brain injury patients with severe regional spasticity with overdose of China-making BTX-A whose trademark is HengLi. The treatment improved spasticity and with little adverse effects. We therefore conclude that overdoses of BTX-A could also be safe and more efficient used in some patients who are showing severe spasticity of limb muscles, but it should be vary with each individual and a large sample size trial is needed for a further confirmation.

Keywords: Botulinum toxins, Type A, Brain injuries, Injections, Drug overdose.

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Introduction

Spasticity often occurs after brain injury and always affects the motor ability and other function of the patient, thereby necessitating intervention in some cases. At present, the most effective method is injection of BTX-A in the spasming muscles. However, there is no unified guideline for the injection doses [1], the highest dosage for a single injection is less than 600 IU in Chinese guideline. So the most usage dose of BTX-A which injected to the spastic muscles of patient, was always 100-500 IU per time of per patient in our clinical work days, and sometimes it seems to take insufficient effects during a period of 2 weeks, the effect of BTA-A even last for more than 3 months.

So in patients with extensive or severe muscle spasm we decided to increase the dose of BTX-A. Although the half-lethal dose of BTX-A is 40 IU/kg of body weight, which implies that a dose of BTX-A over 600 IU is safe, even a larger dose might be safe enough, but it is not confirmed yet, only few trials of small sample has been published, and the doses are less than that we used [2]. Thus, we tried administering higher BTX-A doses in two patients who had developed a severe regional spasticity after brain injury. To our knowledge, none of this kind of reports has been published yet.

Case Presentation

This study was conducted in accordance with the declaration of Helsinki, and it was conducted with approval from the Ethics Committee of the affiliated hospital of Qingdao University. Written informed consents were obtained from the participants. All procedures were performed with the consent of the patients and their family members.

Case 1

A 57-year-old man was admitted because of sudden glossolalia with choking and coughing while drinking, who was also unable to walk and swallow, had an over 10 years history of high blood pressure, but irregular use of antihypertensive agents. He was carried to our hospital for further rehabilitation after a preliminary treatment in a local hospital. Physical examination (PE) at admittance: BP 148/86 mmHg. The systolic pressure was a little higher, and his heart rate, rhythm and both the lungs were heard normal.

Nervous system examination (NSE): Although consciously, but the patient was anepia, depressed, and a little uncooperative on checking. His right nasolabial groove was relatively shallower, and poor tongue controlling. 0-1 grade muscle strength on his right side, and 3-4 grade on the left,

increased muscle tone, and hyperactive tendon reflex, Modified Ashworth Scales (MAS) of both sides are range from 1+ to 2 grade. Right Babinski's sign was positive (+), but the left was doubtful positive (\pm). Thus the patient was diagnosed as brain stem infarction. He was treated by kinesitherapy (occupational and physical training), and swallowing disorder treatment. After 2 weeks of rehabilitation, his sitting balance reached grade 2; He could stand up from bed with one person's assistance, but could not take a step. He experienced difficulty in lifting his feet and obvious spasticity of his right limbs. His MAS for left elbow flexion muscle, right hamstring, and right triceps surae was grade 2, whereas his left triceps surae was grade 1+. After taking Tizanidine (an oral antispasmodic drug) for about one month, with the dose gradually increasing from 6 mg/d to 12 mg/d. However, there was appeared some unexpected symptoms, such as dizziness and/or sleepiness [3].

Thus we decided to administer a local injection of megadose of BTX-A in the severe spasming limb muscles. The right upper flexor muscles and the right lower limb were injected with 250 IU and 450 IU, respectively. We chose 5 muscles as the targets for injection:

1. The adduction muscle
2. Hamstring muscles
3. Triceps surae
4. Posterior tibial muscle
5. And/or flexor digitorum longus

We used surface electrodes to detect the most contracted and sensitive parts of the muscles, marked on the surface then inserted needle electrodes deeply into the muscle to search for the appropriate motor points. Drug preparation: 100 U BTX-A was diluted with 2 ml normal saline to a final concentration of 50 U/ml. 4-6 injection points for a large muscle and 1-2 for small muscles were selected; each point injected 0.5-1 ml (25-50 U) BTX-A. After 4-10 days, the tone of the injected muscles was decreased, and gradually the patient could also stand and take steps in a stable condition. Two weeks to 3 months after injection both the patient's Modified Ashworth Scale (MAS) and independent functional walking ability improved significantly, except a short period of mild weakness of muscle strength, there is no adverse effect occurred.

Cases 2

A 48-year old male was admitted to ICU 2 months after multiple traumatic injuries during a traffic accident. PE: Clear-minded and spoke fluently, but high-level intelligence was impaired, especially the memory and orientation ability, and both of his eyes had limited abduction, hypopsia of counting fingers at a 60 cm distance. The muscle forces for both the upper limbs were grade 4 (MMT), moving with slight fibrillation. The proximal muscle force of the left leg was grade 2, whereas the distal level was 0. The right lower limb proximal muscle force was grade 1 and the distal was grade 0, with increased muscle tone of MAS grade, for the bilateral quadriceps were level 3, and the bilateral adductors were level 2-3. Magnetic resonance imaging (MRI) showed changes after

the traumatic brain injury, including hydrocephalus. Thus the final diagnosis of the patient was "Brain injury, Multiple fractured ribs, Left femur fracture, and Acute suppurative myelitis".

After routine rehabilitation therapy for 3 months, the patient's sitting balance was restored to level 2. He could stand up and sit down with assistance. He could stand but could not move with walking aid. The bilateral iliopsoas muscle forces were 2-3 level. He could walk 3-5 meters on flat ground with the use of bandages and support from two persons. His hips showed obvious bilateral adduction leading to an atypical scissors gait, which made knee flexion and sitting difficult. He was given a little dose of Tizanidine firstly, however, Tizanidine administration was rapidly terminated because of its adverse effects, such as lethargy, low blood pressure [3]. BTX-A injection was then administered to his bilateral adductor muscles and quadriceps femoris at a final dose of 350 U each. The dilution and injection methods were the same as those described in Case 1. After 3-7 days of injection, we evaluated the patients' lower limb muscles spasm degree [4]. The MAS was improved significantly, and the grade of functional walking ability improved at 2 and 4 weeks respectively after the injection, lasting more than 3 months.

Discussion

BTX-A has been used to treat muscle tension disease for more than 50 years, and it has been widely applied by now [5-10]. At present, BTX-A can be made in several countries including China. The commercial name of Chinese BTX-A is HengLi, each vial contents 100 U. BTX blocks the physiological function of cholinergic nerve conduction, especially at the muscle-nerve joints, thus causing voluntary muscle relaxation. BTX-A is one of the most toxic substances in the world. However, after nearly 50 years of clinical application, the safety of BTX-A has been fully demonstrated [11]. A half-lethal dose of mankind is 40 IU/kg, but with a maximum permissible dose of 600 U being the Chinese domestic expert consensus in 2010. As a result, repeated injections may cause immune complex diseases, so repeated BTX-A injection within 3 months is prohibited, but repeated injections have been reported in a short term within 1 week. Repeated injection in a short term is not well understood, and therefore, we do not advocate this approach.

We report two cases with muscle spasms after brain injury, who were treated by injecting BTX-A. Both the injection doses exceed the maximum dose of the Expert Consensus but were far from the median lethal dose. In both cases, no adverse reactions occurred, and the treatment helped achieving better clinical effects than the alternatives, similar to that reported in previous studies [12-14]. Overdosage of BTX-A can be more efficacy and safe enough, therefore, in our further clinical study, according to the individual need and economic characteristics of the patient, we should reasonably and individually adjust the doses of BTX-A to achieve the best therapeutic effect and more beneficial to the patients' self-care ability.

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*Corresponding to:

Jiang Li

Department of Rehabilitation

The Affiliated Hospital of Qingdao University

PR China