USE OF BOTULINUM TOXIN IN SPASTIC CEREBRAL PALSY, REVIEW OF LITERATURE

PRIMENA BOTULINUM TOKSINA KOD SPASTIČNE CEREBRALNE PARALIZE, PREGLED LITERATURE

Marko Aleksić¹², Zoran Baščarević¹²

¹ Institute for Orthopedic Surgery "Banjica", Belgrade, Serbia
² University of Belgrade, Faculty of Medicine, Belgrade, Serbia

Correspondence: marko.aleksich@gmail.com

Abstract

Botulinum toxin type A is a protein that is synthetized by Clostridium botulinum. It represents one of the most potent toxins in nature. It is a cause of poisoning (botulism), but it also has a beneficial effect on reducing muscle spasm and has found widespread use in medicine, with indications increasing year by year. If properly dosed, complications are rare and without major consequences.

In the treatment of spastic cerebral palsy, it is beneficial in reduction of spasm. The effect is localized and systemic side effects are absent. The patient’s acceptance of this therapy is on a high level. The effect on the gait pattern can be maintained at a satisfactory level between 3 and 6 months after administration. The interval between therapies is about 3 months, provided that constant control of motor function of the spastic limb is ensured. Better results are achieved on passive movements than active movements. Effects are transient and reversible.

Therapy should be started at an early age before the development of contractures, because deformity can be prevented.

Botulinum toxin type A therapy is considered to be the pharmacological therapy of choice in the treatment of spastic deformities in patients with cerebral palsy, due to its reversible effects, low rate of side effects, painlessness, and the possibility of repeated therapy.

Keywords: cerebral palsy, botulinum toxin, spastic deformity, electromyoneurography, skeletal muscle
Sažetak

Tip A botulinum toksina je protein koji sintetište bakterija Clostridium botulinum, a predstavlja jedan od najsnažnijih toksina u prirodi. On je uzrok trovanja (botulizam), ali ima i povoljan uticaj na smanjenje mišićnog spazma, te je našao široku primenu u brojnim medicinskim disciplinama, pri čemu se indikacije iz godine u godinu povećavaju. Komplikacije su retke i bez većih posledica, ukoliko se pravilno dozira.

Ima povoljan uticaj na smanjenje mišićnog spazma u lečenju pacijenata sa cerebralnom paralizom spastičnog tipa. Dejstvo je lokalizovano, a sistemski neželjeni efekti se ne javljaju. Prihvatanje ove terapije od strane pacijenata je veoma dobro. Efekat na hod sačuvan je na zadovoljavajućem nivou između 3 i 6 meseci od primene. Interval izmedju terapija iznosi oko 3 meseca, uz uslov da se obezbedi stalna kontrola motorne funkcije spastičnog ekstremiteta. Bolji rezultati primene postignuti su brže na pasivnim pokretima u odnosu na aktivne pokrete. Efekti su prolazni i reverzibilni. Terapiju bi trebalo početi u ranom uzrastu pre razvoja kontraktura jer se tada postižu bolji rezultati i može se sprečiti pojava deformiteta.

Danas se terapija tipom A botulinum toksina smatra farmakološkim sredstvom izbora u lečenju deformiteta kod pacijenata sa spastičnom formom cerebralne paralize zbog svog reverzibilnog efekta, niske stope neželjenih dejstava, bezbolnosti, kao i mogućnosti ponavljanja terapije.

Introduction

Botulinum toxin type A (BTA) is a protein synthesized by an anaerobic bacteria, Clostridium botulinum, and is one of the strongest toxins found in nature (1,2). It is a cause of poisoning (botulism), but it also has a beneficial effect on reducing muscle spasm and has found widespread use in medicine, with indications increasing year by year. If properly dosed, complications are rare and without major consequences. The value of BTA therapy is the possibility of repeated administration, while the weakness of this therapy is reflected in its high cost. It was first used in the treatment of spastic deformities in patients with cerebral palsy (CP) in 1993 (2,3). Koman was the first to systemically administer BTA to children with CP, aged two to eight years (second stage of motor development) (4).

Bacilli of the genus Clostridium that produce Botulinum toxin (BT), are a heterogeneous group of rod-shaped anaerobic gram-positive bacteria that form subterminal endospores. Clostridium botulinum is a ubiquitous microorganism found in soil, marine sediments and the gastrointestinal system of many species of fish, birds and mammals worldwide. Its spores are extremely resistant to environmental conditions and can withstand temperatures of up to 120°C. Under anaerobic conditions, spores germinate and develop into microorganisms that produce the toxin. Although phenotypically distinct, in the past, all organisms capable of producing BT were classified as Clostridium botulinum (5). Today, serotypes A through G are grouped according to the antigenic specificities of their toxins, and some are isolated as separate species. Strains with or without proteolytic activity are also described. Out of the eight different types of toxins (A, B, C1, C2, D, E, F, G), all but C2 belong to the neurotoxin group. Toxins A, B, E (C. butyricum), and rarely F (C. baratii), cause poisoning in humans. Type G is associated with sudden death unrelated to neuromuscular paralysis mechanisms, which has been reported in several cases in Switzerland. Today, this serotype stands out as C. argentinense (6). Types C and D cause disease in animals (7). In humans, this toxin causes poisoning known as botulism. It is a paralytic disease characterized by symmetric, descending flaccid paralysis that begins with the involvement of cranial nerves with distal progression to the trunk and extremities. After ingestion or production in the wound or intestine, the toxin enters the bloodstream and is transported to the peripheral cholinergic nerve endings (including neuromuscular junctions, post-ganglionic parasympathetic nerve endings, and peripheral ganglia), where it inhibits acetylcholine release. This produces paralysis of smooth and transversely striated muscles, as well as exocrine glands. The most common clinical picture includes symptoms of diplopia, dysarthria, and dysphagia, which are accompanied by nausea, vomiting, and abdominal pain, followed by progression to the neck, chest, and extremities, asymmetric muscle weakness, leading to acute respiratory failure (due to respiratory muscle paralysis) and death in the most severe cases (7).

Alan Scott, an American ophthalmologist, conducted first BTA experiments on animals. In 1978, he applied BTA for the first time in humans, in the treatment of strabismus. The tests have proven to be successful, marking the beginning of a series of studies that have examined the effects of BTA in many conditions of muscular hypertactivity over the next decade (1,2,8). The U.S. National Institutes of Health, 1990. declared a consensus officially accepting the clinical use of BT for therapeutic purposes. Today, BTA is commercially available in the form of two preparations: Botox® and Dysport®. Although both preparations contain BTA, the concentration is different, and Botox® has four times the potency in the equivalent dose as Dysport® (9,10).
Botulinum toxin is the most potent of all known neurotoxins. All clostridial neurotoxins are synthesized in their inactive forms as single polypeptide chains of molecular weight of 150 kDa without a leading amino acid sequence, and are therefore thought to leave the cell by a process of bacterial lysis (9). Active neurotoxin is a protein by its structure (150 kDa), consisting of a heavy (100 kDa) and a light (50 kDa) polypeptide chain, which are interconnected by a disulfide bond. It is highly selective for peripheral cholinergic nerve endings containing acetylcholine. By its heavy chain, BT binds rapidly to high-affinity receptors on the presynaptic neuron membrane (11). After binding, the toxin is actively transported through the cell membrane by receptor-mediated endocytosis, into the cell, where it is encapsulated. Within the endosome, BT chains separate. The light chain - a toxic component of BT - is transported to the cytosol. In the cytosol, it binds to a protein associated with the 25 kDa synaptosome (SNAP-25), which is involved in the fusion process of acetylcholine vesicles and the presynaptic membrane. By altering its conformation, it prevents the release of acetylcholine (Ach) molecules, thereby inhibiting neurotransmission. The affected neuromuscular junctions are permanently and irreversibly inactivated. The denervation of the neuromuscular junction also causes anatomical changes: atrophy of the muscle fibers and germination of axonal endings that form new synapses with the surrounding muscle fibers. These reparative processes, including the formation of new neuromuscular junctions, take several weeks or even several months to develop (12).

Like any other drug, BTA carries certain risks. Muscle atrophy occurs during the period of BTA application. The effect is reversible, however, and permanent atrophy has not been reported so far. Repeated applications may result in an increase in the number of fast-contracting muscle fibers (type I fibers with high actin and myosin content) (13). Systemic effects are observed after administration of very high doses or if it is mistakenly injected in the blood vessel during administration. Consequently, botulism-like symptoms can occur, although they are usually less intense and stop after a few days. In most cases, antidote therapy is not necessary. Calcium ion antagonists may inactivate BTA, whereas long-term administration of corticosteroid therapy, as well as some myopathic diseases, may increase sensitivity to BTA (13). Aminoglycoside antibiotics increase the effect of BTA. One of the main reasons for the failure of BTA therapy is the creation of antibodies. The BTA antibodies were demonstrated by bioassay on experimental animals, as well as by ELISA test. The development of antibodies in humans has been reported in 5-10% of patients who have been on long-term BTA therapy. Female patients are at increased risk for antibody production, and greater caution is required when planning therapy. Prevention of antibody formation can be achieved by avoiding the administration of large single doses, with a minimum time interval of three months between applications. Antibody formation may be suspected if there is complete absence of effect after two or more BTA applications (13-16).

Contraindications for the use of BTA are neuromuscular transmission disorders such as Myasthenia Gravis and Lambert-Eaton syndrome, as well as the existence of uncorrectable joint deformities. So far, there is no evidence of adverse effects of BTA during pregnancy (15,16).

Cerebral palsy

Cerebral palsy (CP) can be defined as a non-progressive disorder of cerebral cortex function resulting from a lesion of the central nervous system. Cerebral palsy is classified according to the form of dysfunction and anatomical distribution into a pyramidal or spastic, extrapyramidal and mixed form. The pyramidal form includes spastic hemiplegia, diplegia and quadriplegia, while extrapyramidal forms include athetosis, chorea, dystonia and ataxia. The mixed form has both spastic and dyskinetic features. In contrast to the common spastic syndromes present in central motor neuron lesions in adult patients, spasticity in children with CP may be combined with dystonia (17).

In the treatment process, a multidisciplinary approach is used, combining orthopedic and neurosurgical operative treatment with physical and medicament therapy, alongside neurological and psychological treatment (17).

Botulinum toxin in the treatment of cerebral palsy

Botulinum toxin was first used in spasticity therapy in 1990. Three years later, it was used to treat spasticity in CP. Koman (USA) was the first one to systemically administer BTA in children with CP, aged two to eight years (in the second stage of motor development) (4). BT therapy in patients with CP was used to treat dynamic, correctable, deformities in combination with physical therapy and orthopedic treatment, with the aim of non-operative deformity correction, thus avoiding or at least delaying surgery until the later age (18).

Dosing depends on the BTA product used. For Botox®, the recommended dose is 4-12 IU per kg of body weight, and the maximum dose is 300 IU per treatment (50 IU per injection site). For Dysport®, the recommended dose is 15-30 IU per kg of body weight. The maximum dose administered should not exceed 1000 IU per patient, with a minimum individual dose of 100 IU per muscle (19).

Clinical effects can be expected within two weeks of administration, and during this time any other treatment should be avoided. Injections should be repeated every six to 12 months, but not earlier than three months. It has been shown that it is more efficient and safer to administer higher doses of BTA in less frequent injections, leading to longer-lasting functional outcomes and better patient compliance (20). In the period between injections, active strengthening of spasticity-affected muscle antagonists is encouraged. Spastic muscle relaxation facilitates stretching, promotes growth, prevents contracture, and delays...
surgery. To improve the effect of BTA, the application may be accompanied by short-term casting, intensive physical therapy, and orthoses in order to maximize spastic muscle stretching (21). Pathological contraction in spasticity leads to limited muscle growth. When applying BTA in children with crouched gait, Thompson et al. found that BTA therapy caused increased longitudinal growth and remodeling of targeted spastic muscles. Muscle elongation occurred 6 months after application. In addition, BTA therapy has contributed to improvements in knee extension, gait dynamics, and gait velocity (22).

Evaluation of the effect of Botulinum toxin therapy

Evaluation of the effect of BTA therapy is done using patient questionnaires. Function improvement is recorded with a scale from 0 to 3, where 0 is no improvement and 3 represents maximum improvement. Presence of pain is measured on a scale from 0 to 100, where 0 represents absence of pain and 100 is the maximum intensity of pain. The degree of spasm before and after BTA application can be measured using a modified Ashworth scale. The spasm frequency scale measures the number of daily spasms before and after BTA therapy. On this scale, 0 indicates the absence of spasms, while 4 indicates the excess of 10 or more spasms per day. Evaluation is also done using EMG records before and after the application (21). In addition, other parameters such as gait evaluation, standing, sitting, nursing, dressing, measuring the volume of passive and active movements, radiographic measurements, photographing, and evaluating motion using video and instrumental gait analysis are used in the outcome assessment (18).

In the study by Cobeljic et al, 55 patients were treated by BTA therapy. The results were favorable at application intervals of 3 to 6 months with an applied optimal dose of 10 MU/kg. Favorable results were achieved faster on passive movements than active movements. A slight decrease in active movements was observed after 3 months, and after 6 months of application, there was a 25% decrease in active movements. Passive mobility was maintained throughout the six-month period without significant changes. The positive effect of BTA on gait has been maintained at between 3 and 6 months after administration. A dose of 10 MU/kg proved to be optimal in patients with spastic CP because it led to an improvement in all clinical parameters monitored (18).

There are still several inconsistencies regarding optimal dose, length of time intervals between applications, optimal age to start the therapy, long-term effects on mobility, and side effects that occur with repeated administration over longer periods of time. Further studies are needed to clarify these issues.

Therapy with BTA has many positive features including reversible effects, low rate of side effects, painlessness, and the possibility of many repeated therapies. It is thus considered the pharmacological treatment of choice for dynamic, spastic deformities in young patients with CP (18,23-25).

Final considerations

There are many advantages of BTA therapy over other forms of spasticity therapy: firstly, the effect is localized, meaning that systemic side effects associated with drug administration will not occur. Compliance in this therapy is better than other therapies (22). The effects are transient and reversible. If some negative effects do arise, their effect is not permanent. If the effects are positive - as is most often the case, then easy repetition of therapy, at intervals of 3 to 6 months, will allow the same results to be achieved again. Generally, the interval between therapies is prolonged as much as possible and is usually at least 3 months, provided that constant control of the motor function of the spastic limb is ensured. The degree of muscular spasticity decreases significantly and rapidly after BTA administration, and the achieved effect is maintained for 6 months (18). According to the results of the study by Ubhi et al, therapy should be started at an early age before the development of contractures, because the deformity can be prevented, and thus a long-term benefit to the patient can be achieved (23). Better results are achieved faster on passive movements than active movements. Some deterioration was observed after 3 months, and after 6 months there was a 25% decrease in active movements. Passive mobility is generally maintained throughout the 6 months period, without significant changes. The effect of BTA on gait remains at a satisfactory level between 3 and 6 months after administration. A dose of 10 MU/kg proved to be optimal in patients with spastic CP because it led to an improvement in all clinical parameters monitored (18).

There are still several inconsistencies regarding optimal dose, length of time intervals between applications, optimal age to start the therapy, long-term effects on mobility, and side effects that occur with repeated administration over longer periods of time. Further studies are needed to clarify these issues.

Therapy with BTA has many positive features including reversible effects, low rate of side effects, painlessness, and the possibility of many repeated therapies. It is thus considered the pharmacological treatment of choice for dynamic, spastic deformities in young patients with CP (18,23-25).

Literature


