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USE OF BOTULINUM TOXIN TYPE A IN THE TREATMENT OF SPASTICITY IN CHILDREN WITH CEREBRAL PALSY

Ljiljana Lazić, Hristina Čolović, Olga Marinković, Marija Spalević, Anita Stanković and Dragan Zlatanović

Cerebral palsy has an incidence of about 1-2 per 1000 live births, and in spite of the progress of neonatal medicine, it seems that the incidence will not subside in the near future. The most important characteristic of cerebral palsy is movement abnormality: spasticity, chorea, athetosis, ataxia, dystonia, as well as their different combinations. About 70% of children who suffer from cerebral palsy also suffer from some form of spasticity. Spasticity is a type of muscle hypertonicity characterized by rapid increase in resistance to passive stretching of muscles. The interest for botulinum toxin application in the treatment of spasticity has dramatically increased in the last 10 years. Botulinum toxin is the most powerful neurotoxin that is found in nature. It is produced by anaerobic bacteria – clostridium botulinum. It is produced in eight serotypes of which type A is the most commonly used. Botulinum toxin blocks neuromuscular transmission and causes irreversible weakness of the treated muscle. It has been used since 1993 in the treatment of cerebral palsy in children. The toxin effect is permanent and it results in irreversible denervation. Functional recovery is possible after 2-4 months, due to sprouting of nerve endings and the formation of new synaptic contacts. Treatment with botulinum toxin is safe. Adverse effects are rare, temporary and completely reversible. Application of botulinum toxin prevents or reduces contractures and deformities, and thus delays or avoids surgical treatment. Yet, physical therapy, which prolongs and improves the effects of botulinum toxin, remains an essential and most important form of therapy in the treatment of children with cerebral palsy. *Acta Medica Medianae 2011;50(2):63-67.*

Key words: *cerebral palsy, spasticity, botulinum toxin, children*

Department of Physical Medicine, Rehabilitation and Prosthetics, Clinical Center Niš

Contact: Ljiljana Lazić
Department of Physical Medicine, Rehabilitation and Prosthetics, Clinical Centre Niš
Blvd. Zoran Đinđić 48, 18 000 Niš
E-mail: draganzlatanovic1@gmail.com

Introduction

Cerebral palsy has an incidence of about 1-2 per 1000 live births, and in spite of the progress of neonatal medicine, it seems that the incidence will not subside in the near future. There are numerous definitions of the cerebral palsy, but not one of them is completly adequate and comprehensive. Most definitions highlight: the relative persistence of state and predominantly motor problems (problems of posture and movement), which is a result of early (pre-, peri-, and post-natal) brain damage. Often, in addition to motor problems, a number of associated disorders are present (slow mental development, mental disorders, problems with vision, hearing, speech, epilepsy, etc.).

The most important characteristic of cerebral palsy is the movement abnormality: spasticity, chorea, athetosis, ataxia, dystonia, as well as their different combinations.

Pathophysiology of cerebral spasticity

Muscle tone is regulated by α motor neuron in the spinal cord, and it is normal when there is a balance between the two competitive forces. Those forces are:

- Excitatory impulses are generated in the muscle spindle and Golgi tendon organ then they enter the spinal cord through afferent neuron and release excitatory neurotransmitters such as glutamate and aspartate.
- Inhibitory impulses arise in the basal ganglia, brain stem and cerebellum, then go down the spinal cord and release the inhibitory neurotransmitter - γ-aminobutyric acid (GABA) from interneurons, which then connects to the α motor neuron (1).

In cerebral palsy, part of the brain that produces descending inhibitory impulses is damaged, resulting in the relative "excess" of excitatory impulses and increase in muscle tone.

Spasticity is a type of muscle hypertonicity characterized by rapid increase in resistance to passive stretching of the muscles. It is often accompanied by weakness, hyperreflexia and

clonus. It is present when a person is awake, but it decreases when a person is asleep. It increases with excitement and with voluntary movements when also simultaneous contractions of the antagonist occur. All this results in a movement that is stiff, jerky and imprecise.

Spasticity more often attacks lower in relation to the upper limbs. It also more often attacks flexors, adductors and internal rotators than their antagonists. Around 60 – 70 % of children who suffer from cerebral palsy, also suffer from spasticity, and usually in combination with some other disorder - chorea, athetosis, dystonia. The degree of spasticity varies from medium to heavy, which is, in practice, classified according to the Ashworth scale.

Treatment of these children is reduced to physical medicine and rehabilitation, orthopedical treatment and application of orthotic devices, in order to prevent or treat existing structural defects that occur secondarily because of the presence of neurological lesions (2). Child that will later develop cerebral palsy does not have any deformities or contractures at birth. As child grows and develops, spastic musculature cannot follow the growth of the surrounding structures and tissues. That leads to contractures, deformities and damaged functions. The primary cause of the shortening of the muscle is hypertonia which is always present and long-lasting. In contrast, passive stretching of a relaxed muscle can restore the normal longitudinal growth (3).

In the last decades, great efforts have been made to find an adequate remedy to reduce spasticity. Application of that remedy should relax the over-active muscles. Medications for spasticity reduction that can be applied orally are: baclofen, diazepam and dantrolen. Their application did not show the expected results. When applied in the usual therapeutic dosage, the minimal reduction in spasticity is achieved. If the dosage is increased, the side effects occur (lethargy, drowsiness), and even hepatotoxicity with dantrolen (4). Slightly better effects are obtained by intrathecal application of baclofen, and by selective posterior rhizotomy (5).

In the last ten years, interest in the application of botulinum toxin in treating spasticity has sharply increased. Great number of studies shows positive therapeutic effects of botulinum toxin, with negligible side effects.

Botulinum toxin is the most powerful neurotoxin that is found in nature. It is produced by anaerobic bacteria – clostridium botulinum. A very small amount of the toxin leads to botulism – paralysis with bulbar symptoms, and affects the autonomic nervous system.

History

Botulism was registered in 1822. Back then it was thought to occur as a result of poisoning by fatty acids from sausages. In 1897, van Ermengem proved that it was a bacterial toxin.

In a randomized, controlled study, done on an animal model, it was proven that botulinum toxin A leads to decrease of spasms, and in that way prevents contractures with hereditary spastic mice.

The discovery that botulinum toxin can block neuromuscular transmission and cause muscle weakness became the basis of numerous studies for the use of toxin in therapeutic purposes.

Alan Scott, ophthalmologist, was the first one to use botulinum toxin for strabismus treatment in 1981. After that, there was an expansion of research in various medical fields. Toxin is used in treatment of various diseases: multiple sclerosis, stroke, Parkinson's disease, tremor (essential, cerebellar, etc.), dystonia, myofascial pain syndrome, hemifacial spasm, spasmodic torticollis, migraine, blepharospasm, laryngeal disorders, hypertension m. masseter, the anal fissure, hyperhidrosis, in cosmetics, etc.

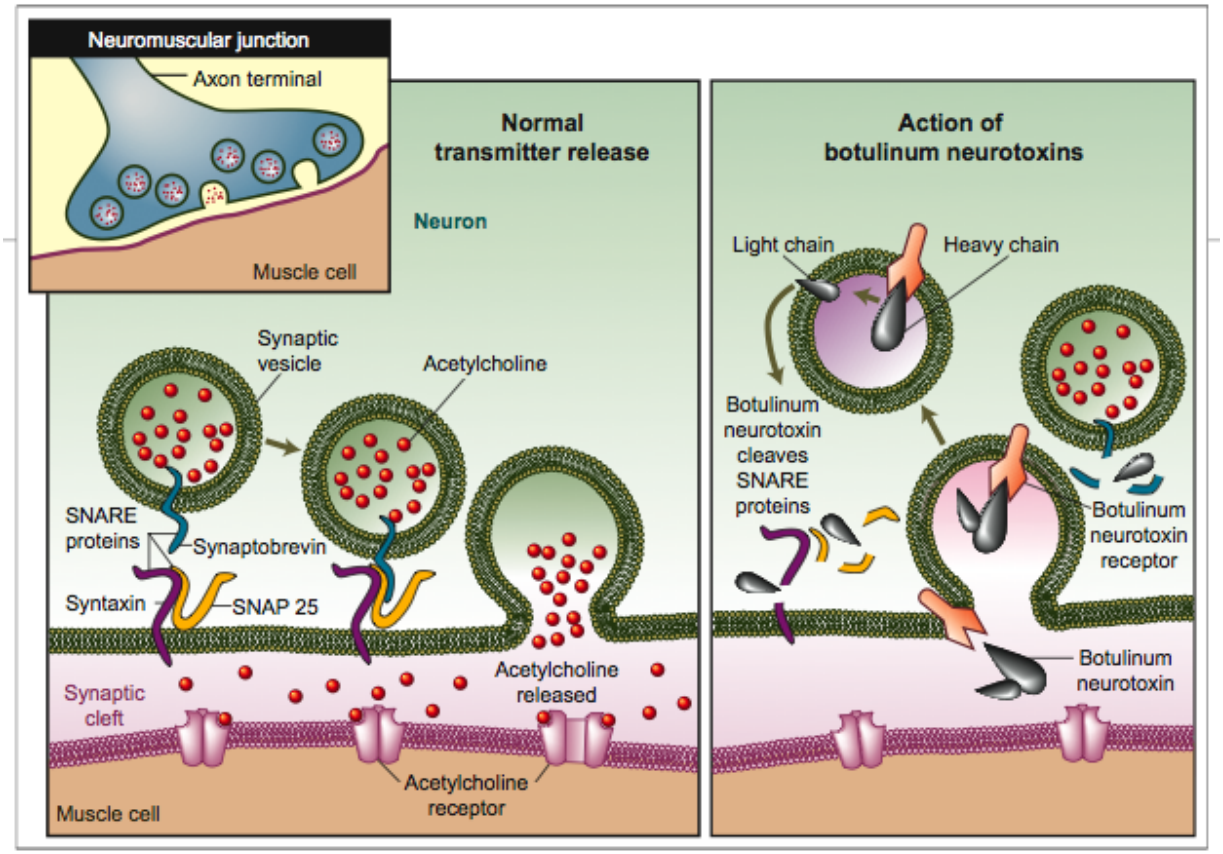
Botulinum toxin was first used in the treatment of spasticity in children with cerebral palsy in 1993. The most common indication is spastic equinus feet.

Mechanism of action

Bacteria Clostridium botulinum produces eight serotypes of toxin (A, B, C1, C2, D, E, F and G). Type A is mostly used in human medicine. They all have similar structure and molecular mass, and they consist of a heavy (H) and light (L) chains that are linked by disulfide bond. Botulinum toxin accumulates in the synaptic end of the cholinergic neuron during the specific process, called endocytosis. After the splitting of the disulfide bond, it separates into two polypeptide chains, and the light one gets the endopeptidase activity. Substrate for the light chain is a cytoplasmic protein SNAP 25 (SyNaptosomal Associated Protein), involved in the exocytosis of synaptic vesicles. Splitting of this protein disables further release of acetylcholine. Mechanism of action is shown in Picture 1. The effect of the toxin is permanent and it results in irreversible denervation. Functional recovery is possible after 2-4 months, due to sprouting of nerve endings and the formation of new synaptic contacts (6).

Application of botulinum toxin in cerebral palsy treatment

Botulinum toxin is used with children with cerebral palsy, with a goal to reduce spasticity, increase the range of motions and improve function (7). It is most commonly administered in the lower extremities and in m. gastrocnemius in the case of dynamic spasticity of equinus feet. If there is a fixed deformity, the use of the toxin is not indicated. Botulinum toxin is also often applied in adductors and muscles of the thigh, while the application in upper limb muscles is rare.



Picture 1. Schematic illustration of the mechanism of action of botulinum toxin, type A

Botulinum toxin is used in children aged 2-6. Toxin dosage is determined by the weight of a child. The usual dosage is 10units/kg if the toxin is applied in one leg or 20units/kg if it is applied in both legs. The maximum dose must not exceed 30units/kg. This dosage is applied with DYSPORT (Ipsen). If another preparation is used (BOTOX), the dosage is different, that is, the units of these two preparations are not comparable and cannot be mathematically converted from one to another (8).

In routine clinical practice, the site for injecting the preparation is determined by palpation. In the case of small muscles (upper extremities), EMG "guidance" is necessary (7).

In most cases, botulinum toxin is applied without sedation and anesthesia. Four to five days after application, it is necessary to start an intensive physical therapy and to use the orthotics (9, 10).

Before the treatment, three weeks after, as well as 3, 6 and 12 months after the treatment, it is necessary to conduct the appropriate checks and measurements, so that the results would be recorded and monitored. Things usually done are: measuring the spasticity according to the modified Ashworth's scale, measuring the range of movement using the standard goniometer, function assessment (using the suitable valid scale for assessment of the motor status), subjective assessment by parents and child. The most prominent therapeutic effect is evident after two to three weeks, the tone reduction is registered (in average 2-3 levels on Ashworth's scale), range of motion is increased (in average 7-15 degrees for dorsiflexion in the ankle), plantar surface during standing is increased, and there is also an improvement in the walking speed, covered distance and the stride length. The effects last from two to four months and after that the application can be repeated (usually botulinum toxin can be applied once, twice or three times).

The botulinum toxin therapy is safe and secure. Side effects are rare, transient, local and completely reversible (11-13). The frequency of side effects after administration of botulinum toxin A (Dysport) was determined based on three prospective studies with 142 patients and 75 patients in the placebo group. Side effects with an incidence greater than 5% were: pain in the leg 8%, pharyngitis 8%, accidental injury 7%, bronchitis 6% and fever 6%. Side effects with an incidence 1-5% were: viral infection 5%, infection 4%, rhinitis 4%, convulsions 4%, infections of the upper respiratory tract 4%, asthenia 3%, asthma 3%, cough 3%, vomiting 3%, colds 2%, diarrhea 2%, unbalanced walk 1%, gastroenteritis 1%, laryngitis 1% and somnolence 1%.

Many of these effects (pharyngitis, bronchitis, fever, viral infection, rhinitis, infections of the upper respiratory tract, cough, vomiting and flu)

had a similar incidence in the placebo group, corresponding to the typical spectrum of diseases in the pediatric population. In addition, the frequency of seizures was identical with the placebo group, which is consistent with the frequent presence of this problem in cerebral palsy. The only significant difference with the placebo group (1%) was with the accidental injuries (falls). This side effect is probably due to excessive weakening of the treated muscle and / or due to local distribution of the preparation to other muscles important for walking. Pain in the leg after application in the placebo group, was present in 5% of the patient. Asthenia and urinary incontinence were associated with higher doses of Dysport (30 units) and could be due to systemic spread of the toxin.

Conclusion

Botulinum toxin, type A treatment of the cerebral palsy in children is an effective and safe way to reduce spasticity and increase mobility. Early treatment of spasticity prevents the occurrence of contractures and deformities, and hence the need for surgical treatment is delayed or even avoided. Comprehensive physical therapy definitely has an important and indispensable role in that prolonging and enhancing the effects of the botulinum toxin A.

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PRIMENA BOTULINSKOG TOKSINA TIP A U TRETMANU SPASTICITETA I KOD DECE SA CEREBRALNOM PARALIZOM

Ljiljana Lazić, Hristina Čolović, Olga Marinković, Marija Spalević, Anita Stanković i Dragan Zlatanović

Cerebralna paraliza se javlja sa incidencom od oko 1-2 na 1000 živorođenih. Uprkos napretku neonatalne medicine, izgleda da incidenca neće opasti u bližoj budućnosti. Najvažnija karakteristika cerebralne paralize jeste abnormalnost pokreta: spasticitet, horea, atetoza, distonija, ataksija ili njihove različite kombinacije. Oko 70% dece sa cerebralnom paralizom ima spasticitet. Spasticitet je tip mišićne hipertonije koji se karakteriše brzim porastom otpora na pasivno istezanje mišića. U poslednjih 10 godina naglo je poraslo interesovanje za primenu toksina botulina u lečenju spasticiteta. Botulin toksin je najmoćniji neurotoksin koji se nalazi u prirodi. Produkuje ga anaerobna bakterija clostridium botulinum u 8 serotipova, od kojih se najčešće koristi tip A. Botulin toksin blokira neuromišićnu transmisiju i izaziva ireverzibilnu slabost tretiranog mišića. Funkcionalni oporavak je moguć nakon 2-4 meseca zbog prorastanja nervnih završetaka i formiranja novih sinaptičkih kontakata. Najčešća indikacija za primenu kod dece sa cerebralnom paralizom je spastični pes equinus. Primenom toksina botulina sprečava se ili ublažava pojava kontraktura i deformacija, a time se odlaže ili izbegava operativni zahvat. Neželjeni efekti su retki, prolazni i reverzibilni. Ipak, fizikalni tretman ostaje nezaobilazan i najvažniji vid terapije u tretmanu dece sa cerebralnom paralizom. *Acta Medica Medianae 2011;50(2):63-67.*

***Ključne reči**: cerebralna paraliza, spasticitet, botulin toksin, deca*