Botulinum Toxin's using in Treatment of Cerebral Palsy

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Abstract: Using botulinum toxin (BTX) to treat CP patients has become more mature and widely used recently. In this article, the authors first briefly introduce the CP and BTX, then summarize the mechanisms of BTX on the treatment of CP through a flow chart, following by opinions driven from recent clinical treatment results. Most articles mentioned by the authors conclude that BTX therapy is one of the most important treatments for CP patients, and the opposed research shows that it is rebuttable. Through careful analysis, the data confirms the effectiveness of BTX therapy in the treatment of CP patients and concludes that BTX treatment should be treated as a supportive treatment monitoring with the involvement of other therapies. Further studies are needed to discover which 1. Impact of cerebral palsy on infant therapy is the best for a company with BTX therapy in different situations.

1 INTRODUCTION

Cerebral palsy (CP), which is a group of disorders that could affect one's ability to move and maintain balance and posture, is the most common motor disability in childhood, about 1 in 345 children has been identified with CP according to CDC's data. Such disorders have symptoms of muscle spasms, stiff feeling, poor muscle control, feeding difficulties and so on, forcing patients to live with assistance equipment like wheelchairs and walking sticks, reducing life quality dramatically. Although CP could not be cured, physical therapy (PT), as the main part of rehabilitation treatment, could improve the situation of patients dramatically. However, the symptom of CP makes the patients under hypertonia situation, making their unable to control the body, including undergoing PT treatment.

Since the hypertonia situation prevent CP patients from PT treatment, which is one of the most direct treatment towards CP, the way of eliminating such negative impact become the hot topic of treating CP patients. Botulinum toxins (BTX), the most poisonous neurotoxic protein know produced by the bacteria "Clostridium botulinum", are discovered by the scientists and seems to become a promising drug for such situation with its two special characters. Firstly, BTX could block the release of acetylcholine neurotransmitter, prevent the transmission of action potential through the neuron system, reduce the muscle stimulation. With lower muscle stimulation, the symptom of hypertonia reduced dramatically. Without hypertonia, patients regain the ability to move normally and undergo the physical therapy. More importantly, scientists discovered that even though BTX is the most poisonous neurotoxic protein, the damage it brings to the neuron system is totally reversible, granting the drug ability to undergo clinical trials. In this review, we highlight the mechanism of BTX under the treatment of CP, examine the research have done so far on the effectiveness of BTX for CP treatment, compare pros and cons of such treatment, and provide our own insight of future treatment directions.

2 IMPACT OF CEREBRAL PALSY ON INFANT

As introduced before, Cerebral Palsy (CP) is defined as motor impairment, including a broad range of

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muscle and movement disorders. The aetiology is mainly attributed to non-progressive disturbances during brain development in foetuses or infants, for example, the lack of oxygen to the brain, gene mutation or head trauma. These injuries can all lead to abnormal development. The injuries can also cause other illnesses. CP is frequently accompanied by impaired cognition, communication and sensory perception, behavioural abnormalities, seizure disorders, or a combination of these features.

According to the main type of movement disorder involved, CP is classified into four main types, depending on which brain areas are affected: spastic, dyskinetic, ataxic, and mixed. Spastic cerebral palsy is the most common type of CP, which affects about 80% of the patients. People with this type of CP have increased muscle tone, which means their muscles are stiff, and their movements can be awkward as a result.

The spastic CP is also described with the body parts that are affected. For example, Spastic diplegia is when the stiffness is mainly in the legs, the arms are less affected or not affected at all. Dyskinetic cerebral palsy means problems are controlling the movements of hands, arms, feet, and legs. Patients would be more difficult to sit and walk due to the involuntary movements, which can either be slow and writhing or rapid and jerky. The ataxic CP stands for problems with balance and coordination. Patients would have a hard time with quick movements. They would be unsteady when walking, actions which require lots of control, such as writing, can also be difficult for them.

Some patients would get mixed CP, which means they would have symptoms of more than one type of CP, a very common type of mixed CP is spastic-dyskinetic CP. The method we introduce in the later text of injecting botulinum toxin (BTX) would only work for the spastic, dyskinetic, and a few mixed CP, as it works by blocking the patient's muscle stimulation.

Once the types of CP have been diagnosed, it is then very important to evaluate the severity of the disease. The Gross Motor Function Classification System (GMFCS) is the most widely used clinical foundational classification of CP. It is an ordinal scale that categorizes a child's mobility or lower limb function in five levels, ranging from walking without restrictions (level I) to inability to maintain antigravity head and trunk postures (level V), below is a summary of the criteria of GMFCS: (Table 1).

Table 1: Level of GMFCS' Criteria.

Grade	CLINICAL MANIFESTATIONS
Level 1	Walks without limitations
Level 2	Walks with limitations
Level 3	Walks using hand-held mobility device
Level 4	Self-mobility with limitations; may use powered mobility
Level 5	Transported in a wheelchair.

3 ILLUSTRATIONS OF BTX AS AN EFFECTIVE TREATMENT FOR CP

3.1 Basic Information about BTX

BTX is produced by Clostridium botulinum under anaerobic conditions and consists of a complex mixture of proteins containing botulinum neurotoxin and various non-toxic proteins. As a neurotoxin, BTX-Type-A(BTX-A) can target and control unpredictable body movement. There are seven different serotypes of BTX, and they could be distinguished by the letters A to G. Different types have a high degree of sequence homology, but their toxicity and molecular action sites are different. Different serotypes bind to different protein receptors. These serotypes inhibit the release of acetylcholine from nerve endings, intracellular targets, action characteristics, and potency. The indirect effects of BTX on the central nervous system are reflex inhibition, reversal of reciprocal inhibition changes, cortical inhibition and somatosensory evoked potential, and formalin-induced pain reduction, suggesting that TB has a direct analgesic effect. In BTX-A, SV2 (isoforms A–C) is the receptor for BTX-A. BTX -A has a complex 3D structure. It is folded into three domains: the heavy chain receptor-binding domain, the heavy chain translocation, and the light chain catalytic domain (Figure 1). It is the most widely studied serotype for therapeutic purposes. BTX interferes with the spinal stretch reflex by blocking the fibres of the fusiform muscle, resulting in reduced afferent signals carried by fibres IA and II and decreased muscle tone. Treating CP with BTX-A can influence the signals to transmit.

3.2 Mechanisms of BTX on the Treatment of CP

BTX injection can reduce muscle spasms. It works as an inhibitor. BTX-A can bind to the presynaptic membrane through gangliosides and protein receptors and then is internalized into the endosome through endocytosis. After this, the light chain is transferred across the membrane to the cytosol, where it acts as a specific endopeptidase against any SNARE (Soluble N-ethylmaleimide-sensitive factor attachment protein receptor) protein. BTX cleaves its substrate before forming the SNARE complex. After BTX-A is incorporated within the early endosomes, the acidic environment of the endocytosis vesicles is believed to induce a conformational change in the neurotoxin structure. The heavy chain is inserted into the synaptic vesicle membrane to form a transmembrane protein-conducting channel that translocates the light chain into the cytosol. After BTX-A is internalized into the cytosol of neurons, BTX-A exerts its toxic effect by virtue of the metalloprotease activity of the light chain. Light chains can specifically cleave three kinds of soluble N-ethylmaleimide. One of the imine-sensitive factor attachment protein receptor SNARE proteins is an indispensable part of vesicle transport and neurotransmitters. BTX-A specifically cleaves SNAP-25 (Synaptosome-associated protein of 25 kDa) at the unique peptide bond. By cutting SNAP-25, BTX-A can block the transmission of some nerve signals in the neurotransmitter and thus act as an inhibitor. Using this specialty, BTX-A is effective in the targeted treatment of CP's uncontrollable muscle tremor, as shown in figure 1.

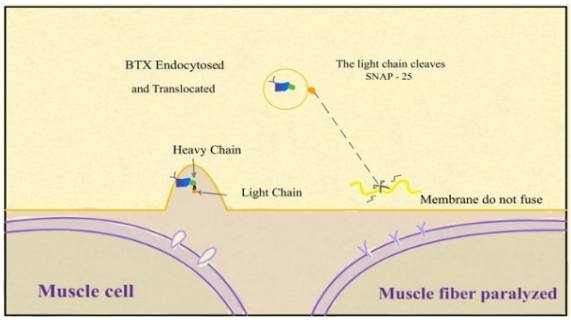

Figure 1: Mechanism of BTX. Mechanism of BTX light chain cleave SNAP-25 then cause muscle membrane do not fuse and the muscle will not be going to be fiber paralyzed.

BTX type A has two different types under the serotype classification, and they could be named by A1LL and A2NTX. According to the article by Norio Akaike et al., when the newly developed BTX-A2 (A2NTX) was injected into the foreleg muscle of a rat, it was transported to the contralateral muscle. This finding is consistent with the retrograde propagation of neurotoxins through spinal cord neurons and then through motor neurons across synapses to reach the contralateral motor neurons in the spinal cord and reach the soleus muscle. The muscle relaxation on the ipsilateral side of the injected toxin was faster and stronger in A2NTX-treated rats than A1LL. This is because A1LL is transported to the contralateral muscle almost equally through nerve pathways and blood flow. A2NTX is mainly delivered to the contralateral muscle through blood. A1LL is more successfully transported to the contralateral spinal neuron than A2NTX. From this, by comparing that A1LL can be transported faster compared to A2NTX. However, the actual use effect of A2NTX may be better than that of A1LL. In an article, people experimented with A1LL could cause a decrease in the grip strength of rats' foreleg, but the A2NTX could not make that. Therefore, the actual use effect of BTX-A1 will be better than BTX-A2.

3.3 Clinical Treatment Result

Pl After it was found that BTX could be a promising medicine for CP patients, researchers almost head to clinical trial directly. That is because BTX has been used to treat different diseases regarding to hypertonia for decades, beginning with the treatment of strabismus in the 1970s. The long history of utilizing BTX to treat hypertonia situations gives physicians rich experiences to handle similar situations. Also, the paralysis caused by BTX could be long-lasting but reversible via the administration of small amounts locally, making such therapy relatively safe to be conducted.

Through years of application in the treatment of CP patients, many clinical data have proven the effectiveness of BTX injection therapy. In 2009, an article conducted by Lukban and colleagues revied cases of class I and class II CP patients, involving 115 children with spasticity of upper limb and 360 children with spasticity of lower limbs. After reviewing the database of such, it concludes that these data provide growing evidence for the effectiveness of BTX treatment in reducing spasticity degrees and could provide a time-limited improvement of function in the upper and lower limbs for children with CP. Another study conducted in 2020 also concludes that BTX therapy has significant improvement in both clinical and

functional outcomes by utilizing different systems to measure functional gains. Through the utilizing of manual ability classification system (MACS) and Canadian occupational performance measure (COPM), such study provides clear and convincing evidence that BTX therapy is one of the most important treatments for CP patients.

Even though some research concluded that BTX treatment is not effective, this research may overlook certain key points. In 2020, an article published by Farag and colleagues denied the effectiveness of BTX in the field of CP; it reports that although there is a positive effect for spasticity degrees after BTX injection treatment for upper limbs spasticity in children, the effect with respect to the function gains or improvement of quality of life remained insignificant or conflicting. Such conclusion seems to be convincing, but researchers actually overvalued what BTX really supposed to do. What BTX treatment could do is to reduce the spasticity degrees for the patients, which does not necessarily mean that could improve the life quality or function situations of patients. Rehabilitation training like walking and running should really take charge of improving patients' quality of life. For CP, it is not that a single therapy or medicine could cure the diseases on its own, it has to be the way that many therapies are used together alone the way. For these patients who could not walk or run because of hypertonia, BTX therapy could eliminate the hypertonia situation as much as possible; however, for these who have never walk or run for their entire life, it is fair to assume that they could not gain the function even without hypertonia situation, which means that there should be someone here teaching them how to do that, and rehabilitation treatment would be "the person" to do that. In conclusion, BTX therapy grants patients the possibility to walk or run, but it does not teach them how to walk or run. In this article, the result has already proved the effectiveness of BTX therapy, and the analysis on functional gains and quality of life seems to be too far ahead.

As mentioned previously, for treatment of CP, it is not that a single therapy or medicine could cure on its own; most of the time, a combination of therapies is so important that it could directly affect the result from experiments. In 2019, a trail performed by Cahlin and colleagues led to the conclusion that the effect of BTX-A compared with placebo on outcome variables was unsignificant at the group level and the evidence could not prove the used of BTX-A as a therapy of affected masticatory muscle in CP. While in 2017, a study conducted by Dursun and colleagues regarding to the treatment of spastic equinus foot due to CP leads to the conclusion that BTX-A injection treatment with physical therapy provided additional benefit for the patients. One significant difference between these two experiments is that the latter experiment conducts more than BTX treatments but also physical therapy along the way. More importantly, even though the former experiment leads to the conclusion that there is no objective improvement, researchers reported that most patients request for continuing BTX injection treatment, implying that there is a subject effect on patients. One plausible explanation would be that patients feel better while undergoing other treatments after BTX eliminates the hypertonia situation. Through the comparison, the importance of the combination of different therapies has been revealed.

Above all, many clinical research have proven the effectiveness of BTX therapy as a treatment for CP patients. Although some research may provide contradictory evidence, there are certain points that we should be aware of, and further research are needed. One example here would be the combination of different treatments with BTX therapy, and such a topic should be something researchers want to focus on in future studies.

4 CONCLUSIONS

In conclusion, here provides information for how CP affects infant and a flowchart for how BTX therapy could be a treatment to eliminate such effect. There are convincing evidences used from other articles that BTX therapy could be one of the most important treatments for CP patients. Evidence shows that there are some opposed conclusions could be driven by overlooking certain key points and combining BTX therapy with other therapy like physical therapy or hydrotherapy is the best way to monitor.

For future research, the study design for BTX therapy should treat it as supportive therapy and involve it with other therapy in order to produce the maximum positive effect for the patients because it is too demanding to test whether a supportive therapy could play an important role alone. Also, more research should be done to discover which therapy is the best for the BTX therapy company.

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