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REVIEW PAPER

Przemysław Nowak [1(ABDFG)], Luiza Balicka-Adamik [2(BDFG)], Katarzyna Stybel [3(BDFG)]

Therapeutic possibilities of botulinum toxin in neurological disorders – treatment of limb spasticity in the course of brain damage

[1] Medical Care Centre, Jarosław, Poland
[2] St. Padre Pio's Regional Hospital, Przemyśl, Poland
[3] Faculty of Medicine (Student), Medical University of Warsaw, Warsaw, Poland

ABSTRACT

Introduction. Botulinum toxin is produced by the anaerobic bacterium *Clostridium botulinum*. The sporulation form of the *C. botulinum* is widely found in the environment (in soil) and may develop in inappropriately stored food. The symptoms of poisoning occur 18-36 hours after consumption of contaminated food.

Aim. The aim of this study is to present the benefits of using botulinum toxin in the treatment of spasticity of the upper and lower limbs in both adults and children.

Material and methods. A literature review of the following databases was carried out: PubMed, UpToDate.

Results. Botulinum toxin interferes with neural transmission by blocking the release of acetylcholine and causes muscle paralysis. The typical symptoms are diplopia, xerostomia, enteroparesis, speaking and swallowing disorders, as well as paralysis of respiratory muscles which leads to death. However, botulinum toxin is also a very potent medication. The biggest application is found in the field of neurology, *inter alia*, in the treatment of spasticity.

Conclusion. The study provides current evidence regarding the safety and efficacy of botulinum toxin injection for spasticity of the upper and lower limbs. Botulinum toxin injections are applicable in the treatment of many neurological disorders and the list of indications will certainly become wider.

Keywords. botulinum toxin, neurology, spasticity

Introduction

History of botulinum toxin

Botulinum toxin was discovered by a German doctor, Justinus Kerner, who carried out experiments with botulinum toxin. In 1820, Kerner published his first monograph on sausage poisoning entitled 'New observations on the lethal poisoning occurring so frequently in Württemberg through the consumption of smoked sausages'.[1] Later, he began animal experiments and experiments on himself to isolate the unknown toxin from sausages.[1] These results were published in a second monograph in 1822 entitled 'The fat poison or the fatty acid and its effects on the an-

Corresponding author: Przemysław Nowak, e-mail: przemeknowakneurolog@gmail.com

Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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imal organism, a contribution to the examination of the substance which acts toxically in bad sausages'.[1] In 1946, Edward J. Schantz created the first clinical product using the crystallization techniques.[1] Allan Scott was the first to use the toxin to treat strabismus patients - from this episode, the first name of the toxin was Oculinum. Approval by FDA (US Food and Drug Administration), National Institutes of Health, and American Academy of Neurology, was obtained in 1989 to market Oculinum for clinical use in the United States for the treatment of adult (patients over the age of 11 years) strabismus, blepharospasm and hemifacial spasm.[1,2] Since 1989, the effectiveness of botulinum toxin A in reducing spasticity after stroke has been demonstrated, with reversibility and low prevalence of complications, obtaining the approval of the US Food and Drug Administration and European regulatory agencies for this indication.[3] Nowadays, there are eight types of botulinum toxin, labelled A–G, but only types A and B are used for treatment.[4] In Poland, botulinum toxin has been used since 1991. On the market, three 'A' types of preparations are available, although none of them is a generic form. They differ from one another according to the protein content, the number of units and potency.

Botulinum toxin in the field of neurology

In neurology, botulinum toxin is injected into affected muscles or glands using a needle. Before the injection, botulinum toxin must be dissolved in 0.9% saline solution.[4] Injection of botulinum toxin into affected muscles blocks the presynaptic release of acetylcholine from motor endplates of the lower motor neuron at the myoneural junction, and decreases tone by limiting muscle contraction.[5] Intraglandular administration of botulinum toxin acts at the neuroglandular junction to block the secretion of saliva and sweat by inhibiting the release of acetylcholine from presynaptic motor neurons.[4] Botulinum toxins A and B interfere with SNARE protein complex.[4] Botulinum toxin A cleaves the host protein SNAP-25, whereas botulinum toxin type B cleaves synaptobrevin.[4,6] The cleaved SNAP-25/synaptobrevin is unable to mediate fusion of vesicles with the host cell membrane, and it is impossible to release the neurotransmiter acetylcholine from axon endings.[4,6]

The biggest application of botulinum toxin has been found in neurology.[7-11]

The mechanism of the action of botulinum toxin can be described as chemical denervation. The beginning of the action is observed 2-5 days after the administration of botulinum toxin and lasts for 2-3 months.[12] The restoration of muscle function is related with reinnervation and formation of new synaptic contacts (sprouting of nerve terminals).[4]

Botulinum toxin is also used for the treatment of pain syndromes affecting secretion of pain mediators (substance P, glutamate and calcitonin gene related protein (CGRP)) from the nerve endings and dorsal root ganglions, reduces local inflammation around the nerve endings, deactivates the sodium channel, and exhibits axonal transport.[13]

There are few contraindications which refer to the administration of botulinum toxin. The most important are: conditions which show disorders connected with neuromuscular transmission, myasthenia gravis, Lambert–Eaton myasthenic syndrome, pregnancy and breast-feeding, allergy to medication, and infections at the injection site.[14]

Botulinum toxin should not be combined with aminoglycosides, penicillamine, quinine, chloroquine and hydroxychloroquine, calcium channel blockers and blood thinning agents e.g. warfarin or aspirin.[14] Anticoagulation only marginally increases the hematoma frequency, provided INR is controlled and appropriate injection techniques are used.[15] Caution should be exercised while administering botulinum toxin to patients with amyotrophic lateral sclerosis, neuropathy, myopathy, dysphagia, respiratory failure or low body weight. Although botulinum toxin is a strong neurotoxin it is a safe medication. The most common adverse effects are injection pain and local oedema, erythema, transient numbness, headache, malaise or mild nausea.[14] The most feared adverse effect is temporary weakness/paralysis of nearby musculature caused by the action of the toxin.[14] The weakness induced by injection with botulinum toxin A usually lasts about three months.[14] Patients receiving injections into the neck muscles for torticollis may therefore develop dysphagia.[14] This usually lasts a few days or weeks.[14] Other systemic side effects include an influenza-like illness and brachial plexopathy.[14]

An important problem arising from the administration of botulinum toxin seems to be systemic immunization with the formation of antibodies against the proteinaceous molecules of botulinum toxin, which leads to resistance to treatment.[16] Patients who receive higher individual doses or frequent booster injections seem to have a higher risk of developing antibodies.[14] It is important to distinguish between immunogenicity and the clinical classifications of secondary non-response (patient initially responds to therapy, but then loses clinical responsiveness over time with repeated injections) and primary non-response (patient fails to respond to the first and any subsequent administration of a therapy).[16]

During the last 30 years, since botulinum toxin started to be applied in the treatment of neurological disorders, the list of indications has become wider. It is undoubtedly a breakthrough in the treatment of many neurological symptoms and disorders where previously, before the 'botulinum toxin's era', medicine was found to be helpless.

The reason for the increased therapeutic application of botulinum toxin A is due to its marked prolonged clinical efficacy and proven safety record.[17]

A definite limitation in the treatment using botulinum toxin is the cost of therapy. The medication is expensive, and additionally requires frequent injections. In Poland, the National Health Fund (NFZ – Narodowy Fundusz Zdrowia) reimburses the cost of treatment of some disorders. There are four treatment programs:

1. Treatment of spasticity in cerebral palsy.
2. Treatment of focal dystonia and hemifacial spasm.
3. Treatment of upper limb spasticity after stroke – since 2014.
4. Treatment of lower limb spasticity after stroke – since 2017.

Application in neurology:
DYSTONIAS
- Blepharospasm
- Torticollis
- Mogigraphia
- Hemifacial spasm
- Laryngeal dystonia, dysphonia
- Bruxism
- Meige's syndrome
- Dystonia which is responsive to L-dopa
- Dystonia musculorum deformans
- Idiopatic and symptomatic dystonias

SPASTICITY
- After craniocerebral and spinal trauma, after ischemic and hemorrhagic stroke
- In multiple sclerosis
- In cerebral palsy

Spasticity is a velocity-dependent increase in muscle tone as a part of the upper motor neuron syndrome and is seen in a wide variety of neurologic diseases.[18] The most frequent causes of damage to the upper motor neuron in adults include: stroke, injury and multiple sclerosis. In children, the most frequent cause of spasticity is cerebral palsy (CP).[19] The Modified Ashworth Scale is commonly used to grade spasticity. It is useful for the assessment of specific muscle groups before and after botulinum toxin administration. The medication can be injected into the specified site under USG supervision.[20-23] It ensures safety and precision of the application. In some cases, EMG can also be used. A prospective, blinded study in Denmark showed that botulinum toxin treatment guided by EMG improves the outcome of the treatment of torticollis.[24]

HEADACHES
- Migraine
- Neuralgia
- Tension headache

CHRONIC PAIN SYNDROMS
- Pain of the small of the back which is connected with increased muscle tone
- Fasciomyalgia
- Fibromyalgia
- Syndromes with neuromuscular conflicts
- Local pain syndrome

AURICULOTEMPORAL SYNDROME (FREY'S SYNDROME)
FACIAL NERVE PARALYSIS
NYSTAGMUS
DRY EYE SYNDROME
SIALORRHEA
ESSENTIAL TREMOR
STIFF-PERSON SYNDROME
NEUROGENIC BLADDER
MYOCLONUS OF PALATE
EXCESSIVE SWEATING

Clinical application of botulinum toxin in other fields of medicine

Botulinum toxin is also used in other medical specialties, not only in neurology.

In ophthalmology: strabismus, nystagmus, oculomotor disorders.[25,26]

In gastroenterology: swallowing disorders, achalasia, pyloric stenosis, Hirschsprung's disease, dyskinesia of biliary tracts, anal fissure.[27-29]

Botulinum toxin treatment

Botulinum toxin type A is a first-line treatment for post-stroke spasticity.[30] Its injection into the muscles brings about satisfactory outcomes, which has been confirmed by many studies.

In one of the randomized, placebo-controlled, double-blind trials conducted by the International Abobotulinum toxin A Adult Lower Limb Spasticity Study Group, the effectiveness was compared between the effect of abobotulinum toxin A and placebo, with respect to the reduction in the lower limbs muscle tone in adult patients who ≥ 6 months ago had undergone stroke/brain damage.[31] It was confirmed that in the case of chronic hemiparesis, a single administration of abobotulinum toxin A decreased muscle tension.[31] The subsequent injections of abobotulinum toxin A during the year were well tolerated by patients, and improved the speed of walking on foot, and the probability of adjustment to the social conditions.[31]

In a systematic review and meta-analysis of studies concerning the use of abobotulinum toxin A in the treatment of lower limb spasticity of various etiology, published in Medicine*, from among 295 records, six randomized clinical trials were selected and evaluated which verified the action of abobotulinum toxin A.[32] The data collected from these studies provided a scientific basis for the use of abobotulinum toxin A in order to reduce spasticity in the muscles of the lower limbs.[32] A statistically significant reduction in the muscle tone

versus baseline values was achieved for the majority of evaluations performer using the MAS (Modified Ashworth Scale).[32]

At present, abobotulinum toxin A is the only preparation accepted by the US FDA for the treatment of lower limb spasticity in pediatric patients aged ≥ 2 years.[33] Intramuscular administration of abobotulinum toxin A has been approved, based on the results of phase 3 of clinical trials in children with lower limb spasticity caused by cerebral palsy.[33] In this sample, a single cycle of treatment was applied using abobotulinum toxin A at a dose of 10-15 U/kg/leg injected into the gastrocnemius muscle and the soleus, considerably improved the tone in the ankle plantar flexor muscle (the main end point).[33] In the recipients of abobotulinum toxin A, a significant response to treatment was observed, compared to placebo.[33]

A randomized double blind controlled trial carried out to determine the safety profile of Incobotulinum toxin A in children with cerebral palsy and gastrocnemius muscle spasticity, demonstrated that there were no significant differences in the frequency of occurrence of adverse effects, compared to the administration of abobotulinum toxin.[34] The study included 35 patients aged from 3-18 years, who were divided into two groups – the control group – 18 children, and the study group – 17.[34]

A systematic review of literature concerning the use of abobotulinum toxin A in the treatment of lower limb spasticity after stroke in adults showed, based on 9 of 12 randomized clinical trials, the high efficiency and safety of such a treatment.[35] The doses of the toxin were from 500 – 1,500 U.[35]

As mentioned above, botulinum toxin is also used in the treatment of spasticity in the course of cerebral palsy. Cerebral palsy is the most common musculoskeletal disability in childhood[36], and it has a worldwide incidence of approximately 2-2.5 cases per 1,000 live births.[37] It is classified physiologically on the basis of predominant tone into spastic, choreoathetoid and ataxic types, with spastic type being the most common, accounting for 80% of the cases.[37] In a Japanese study, sequential physical changes were examined after injection of botulinum toxin A.[38] Nine children with cerebral palsy participated in the study.[38] Measurements were taken of the maximum bending angle and maximum extension in the hip, knee, and ankle joints, step length, walking speed; the observed speed was determined using the Foot Contact Scale (FCS) and the Physician's Rating Scale (PRS).[38] The lower limb range of motion (ROM), Modified Tardieu Scale (MTS), knee joint extension torque, and Gross Motor Function Measure-66 (GMFM-66) were also measured.[38] The measurements were performed before treatment, after 4, 8 and subsequently 12 weeks.[38] A significant increase in the outcomes of treatment with respect to measurements in the ankle joint were observed after 8 weeks, and in the knee joint after 12 weeks. This demonstrates that the effects of action of botulinum toxin do not occur instantly at early stages of treatment.[38]

However, this is not the only study which proves the effectiveness of administration of botulinum toxin in the treatment of spasticity in the course of cerebral palsy. In the study presented below, injections of botulinum toxin A were performed under USG control in muscles of the lower limb (adductor longus, gracilis, medial hamstring muscles, gastrocnemius and soleus).[39] The dose of toxin did not exceed 12 IU/kg.[39] The study included 25 children aged from 3 - 16 years, suffering from unilateral (2) or bilateral cerebral palsy (23).[39] Spasticity in the knee and ankle joints decreased at week 4 and 12 of control, compared to the period prior to treatment.[39] After 12 weeks, spasticity in the hip joint was also reduced.[39] An improvement of the motor functions according to the Gross Motor Function Classification System was observed at weeks 4 and 12 after the administration of botulinum toxin A.[39] During the whole procedure, no adverse effects were noted.[39] In addition, 3 patients, when asked about the perception of pain accompanying spasticity, mentioned that this pain decreased after treatment.[39]

A study was also conducted in Poland to determine the effectivness of repeated administration of botulinum toxin to children suffering from cerebral palsy. In 2004–2010, 60 children with spastic cerebral palsy, aged 2–16, were treated with abobotulinumtoxin A injections (in the gastrocnemius and soleus muscles).[40] Thirty patients were diagnosed as tetraplegic, 20 diplegic, and 10 hemiplegic.[40] In each patient, muscle tone was rated by the Modified Ashworth Scale, passive range of motion in ankle joint, with extended, and flexed knee joint and gait using the Physician Rating Scale.[40] Assessment was performed before and after 8 injections (average dose of injection - 13.2 j/kg/mc).[40] The study showed that the abobotulinumtoxin A injections were effective in children with cerebral palsy, regardless of the number of sessions.[40] The best results were obtained in children under the age of 7 with hemiplegia, and greater impairment than level I on the Gross Motor Function Classification System scale.[40] It was proved that the treatment gain was highest up to 3 months after the injection, and for this reason abobotulinumtoxin A therapy can be safely and effectively repeated every 3–6 months.[40]

Also, a study concerning treatment of spastic equinovarus foot in 23 patients who had undergone stroke, confirmed that an improvement in mobility may be observed 4 and 12 weeks after the injection of botulinum toxin A under USG control.[41] The injections were performed into the following muscles: gastrocnemius, soleus and tibialis posterior.[41] The BoNT-A was injected at 2 sites, with 25 U each for the GC medial head, GC lateral head, S, and TP.[41] No adverse effects were observed in any of the patients.[41]

Botulinum toxin is recommended for use in many clinical cases, and although there is still no consensus about the moment when therapy with the toxin should be undertaken, and how long it should last; nevertheless, it is considered a first-line treatment in the case of focal spasticity.[42] In order to adjust the proper dose of the toxin, it is necessary to regularly monitor the degree of increased muscle tone.[42] The most commonly applied scale is the Modified Ashworth Scale (MAS), where the resistance while passive muscle stretching is assessed at 5 points according to an ordinal scale).[42] However, this scale is not sufficiently reliable, because it has no standardized speeds of elongation of the muscle fibers, does not provide the determination of an overall muscle resistance and, to a great extent, the result depends on the method of performing the examination by a physician. In addition, it concerns only the distal parts of the body, and is not sensitive to slight changes in the muscle tone. The instrument which enables, in a painless and non-invasive way, a quantitative and objective assessment of the properties of muscles is the MyotonPRO®.[42] An article published in Toxins® concerned a retrospective study conducted in order to confirm the safety and effectiveness of the use of Incobotulinumtoxin A at doses from 100 – 1,000 UI in the treatment of spasticity, according to the individual needs of patients.[42] The patients were divided into 3 groups, according to the dose of botulinum toxin A they received. During observation, some patients were assigned to another group due to an increase in the dose of the toxin administered.[42] It was confirmed that a long-term therapy with Incobotulinumtoxin A at a dose up to 1,000 UI is safe.[42] The reported adverse effects, such as transient generalized weakness or dysphagia, were rare.[42] Moreover, the study proved that a repeated long-term therapy (2 years) with botulinum toxin A does not lead to any reduction in the clinical efficiency caused by the formation of antibodies against botulinum toxin A, and/or auxiliary substances in a pharmacological preparation.[42]

Conclusions

This systematic review of studies concerning the use of botulinum toxin in the treatment of spasticity of various etiology, both in adults and children, confirms the great benefit from the introduction of botulinum toxin into the treatment.

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