IRSTI 34.39

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Examples of Clinical Use of Botulinum Toxin: A Literature Review

Abstract. *Botulinum toxin (BoNT), being one of the most toxic substances known to mankind, due to its unique mechanism of action is used as an effective treatment for many diseases, including strabismus, blepharospasm, and hemifacial spasm. BoNT has received particular use as a long-acting analgesic due to its ability to inhibit the exocytosis of pain neuropeptides, including CGRP, Substance P, and modulate the expression of pain-related receptors as TRPV1, NMDA, AMPA, P2X3. Botulinum toxin injections are effective in the treatment of many pain conditions: diabetic neuropathy, chronic migraine, spinal cord injury. This article reviews the possibilities of clinical applications of botulinum toxin based on the analysis of articles in the PubMed database for specific search terms. The keywords "botulinum toxin", "treatment", "clinical use", "pain reduction" were used to obtain references. The possibilities for the clinical use of botulinum toxin are growing every year. Currently, at least 8 commercially available preparations of botulinum toxin types A and B are known, the most recognizable of which are Botox, Dysport, and MyoBloc/NeuroBloc. Future research should focus on improving the safety profile and increasing the efficacy of botulinum toxin-based drugs. New types of botulinum toxin obtained through molecular reengineering will significantly increase its therapeutic efficacy.*
Keywords: *botulinum toxin, clinical use, chronic pain, pain relief, analgesic, migraine, diabetic neuropathy.*

DOI: 10.32523/2616-7034-2023-143-2-81-90

Introduction

Botulinum neurotoxins (BoNT) are a family of neurotoxins produced by strains of Clostridium bacteria that cause severe flaccid paralysis botulism. Human botulism can be contracted in three ways: by ingestion, inhalation, or through a wound. In severe cases, botulism leads to death from respiratory paralysis. There are at least 7 different serotypes, from BoNT/A to BoNT/G. They all act by cleaving SNARE proteins, a tetrahelical complex required for the exocytosis of neurotransmitters into the synapse [1].

Structure and mechanism of action of BoNT

All serotypes of botulinum neurotoxins have a similar domain structure (Figure 1A). The gene encoding the toxin is expressed as a single-chain polypeptide of about 150 kDa [2]. There are three distinct functional domains in native BoNT. The carboxy-terminal domain is responsible for neurospecific binding, the central domain is involved in membrane translocation, and the amino-terminal domain is endopeptidase cleaving proteins involved in the release of neurotransmitters and neuropeptides [3].

The similar structure provides a similar mechanism of action, which is conventionally divided into 4 stages: binding, internalization, membrane translocation and enzymatic cleavage of the target proteins. Studies indicate the involvement of polysialogangliosides and synaptic vesicle proteins in the binding of various BoNT serotypes [4]. Internalization of BoNT occurs by endocytosis of synaptic vesicles. Vesicles containing BoNT are oxidized to low pH values (4.40–4.60), which causes conformational changes in the toxin, incorporation of the translocation domain into the membrane in the form of an ion channel, and translocation of the amino-terminal endopeptidase into the cytosol [5],

which then target proteins depending on the BoNT serotype. BoNT serotypes cleave different intracellular proteins of the SNARE complex or cleave the same protein but in different locations. Botulinum toxins inhibit SNARE-mediated exocytosis by each cleaving specific target proteins: VAMP (vesicle-associated membrane protein), SNAP-25 (25 kDa synaptosome-associated protein), and syntaxin (Figure 1B) [6]. According to different molecular targets, botulinum toxin serotypes have different durations of action. In particular, botulinum neurotoxin A (BoNT/A) has the longest duration of action and is therefore the most commonly used in practice [7].

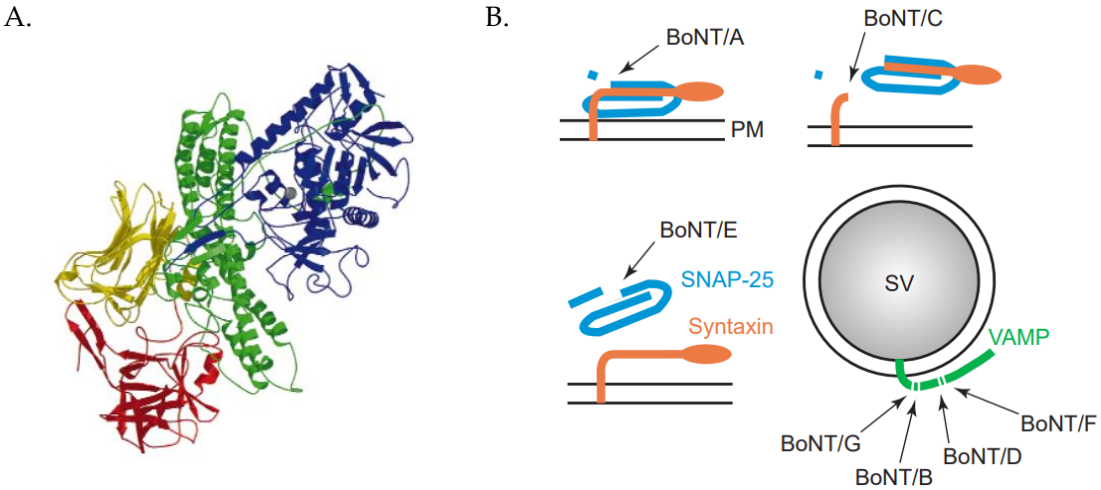

Figure 1. The 3D structure and molecular targets of action of Botulinum Neurotoxin A

(A) The catalytic domain is colored in blue, the translocation domain in green, the binding domain in yellow and red. The catalytic zinc is depicted as a ball in gray [8].

(B) Cleavage sites of BoNTs on the presynaptic membrane and synaptic vesicle (SV) [6].

Molecular explanation of clinical use

Native BoNTs are highly active in neuromuscular synapses due to the expression of specific receptors on the presynaptic surfaces, as well as the relatively large size of the presynaptic endings on muscle fibers. This allows the toxin to migrate in high doses by endocytosis specifically to the motor motor nerve endings [9]. Inhibition of the release of acetylcholine and inhibition of the neuromuscular junction, in turn, is the molecular explanation for the clinical use of botulinum toxins in treatments of muscle spasms and also the hyperfunction of certain excretory glands.

Importantly, botulinum neurotoxin can be considered as a tool to control chronic pain. SNARE-mediated (Soluble N-ethylmaleimide-sensitive factor Attachment Protein Receptor) exocytosis influences the onset and development of chronic pain in various ways. First of all, the fusion of synaptic vesicles filled with pain neurotransmitters and pain neuropeptides with the presynaptic membrane occurs due to the formation of the SNARE complex [10, 11]. Moreover, surface expression of nociceptive receptors also depends on SNARE-mediated exocytosis [12, 13]. Therefore, it is believed that the analgesic effect occurs in the periphery by blocking the release of pronociceptive transmitters and receptors. BoNT reduces the amount of released glutamate, CGRP, substance P, as well as TRPV1, NMDA, AMPA, P2X3.

Methods

A review of the English-language literature was conducted using the PubMed database on October 28, 2022. The following terms were the keywords for the search: “botulinum toxin”, “treatment”, “clinical use”, “pain reduction”. Articles describing the use of botulinum toxin for pain control were selected, analyzed, and summarized, starting from the first mention of the clinical use of

this toxin, i.e. 1973.

Results and discussion

The idea of clinical use of botulinum toxin arose in 1822 from the discoverer of this toxic compound – Justinus Kerner [14]. He predicted the usefulness of injections of toxin in diseases resulting from hyperexcitation of the nervous system. The first attempt to use botulinum toxin clinically was made in the search for a non-surgical treatment for strabismus. Scientists at the Smith Kettlewell Eye Research Institute, led by Alan Scott, published the results of their study in 1973. They demonstrated that administration of low doses of BoNT/A to the oculomotor muscles of *Macaca mulatta* was effective both in the initial and repeated injections [15]. Further clinical studies confirmed the effectiveness of using botulinum toxin in strabismus [16, 17], blepharospasm [18], hemifacial spasm [19]. Treatment of such conditions with botulinum toxin not only effectively reduces the frequency and intensity of involuntary muscle contractions, but also reduces the pain associated with these disorders.

A preliminary pilot study conducted by a group of scientists led by Andrew Blitzer in 1993 proposed a new treatment option for patients with hyperfunctional facial wrinkles [20]. This assumption was verified a year later in a double-blind, placebo-controlled study in which 81% of patients noted a significant improvement, 19% - a moderate improvement in the severity of facial wrinkles after botulinum toxin injections [21].

As a result of observation of patients with hemifacial spasm treated with botulinum injections, the hypothesis of the use of BoNT/A as an agent to combat focal hyperhidrosis has arisen [22]. Since then, numerous studies have confirmed that topical botulinum toxin therapy for axillary, palmar and plantar hyperhidrosis is an effective, simple and fast procedure [23, 24, 25].

Hypersalivation is another autonomic disorder that can be treated with botulinum toxin. It is hypothesized that injections of BoNT/A into the parotid salivary glands may be suggested for patients whose salivation does not respond to medical treatment [26]. A few years later, an article by British scientists was published, according to which injections of botulinum toxin into the salivary glands can serve as an effective and simple method for treating excessive salivation, including in Parkinson's disease [27]. In 1999, positive results of the use of botulinum toxin to reduce abnormal secretion of tears were published, according to which the therapeutic effect lasts for about 6 months [28].

Botulinum toxin has found use in the treatment of disorders of the excretory and gastrointestinal systems. Thus, with detrusor-sphincter dyssynergy, a single injection significantly improved the condition of patients for 3 to 9 months [29]. Botulinum toxin injection results in effective long-term relief of symptoms in 75% of patients with achalasia [30], and complete healing of the anal fissure within 3 months in 82% of patients with sphincter spasm [31].

The first clinical evidence of the antinociceptive action of botulinum neurotoxin arose as a result of the following observations: pain was significantly reduced at small doses insufficient for paralysis, pain relief lasted longer than the period of paralysis, occurred before it, or was the only result of treatment. Thus, according to Stell et al., in some patients treated for spasmodic torticollis, pain relief was present even when there was no correction of the hemorrhage [32]. According to the results obtained by Relja and Klepac in 2002, the antinociceptive effect of BoNT/A on spasmodic torticollis pain appears 7 days earlier than the positive effect on motor function. Additionally, it was demonstrated that the dose sufficient to control pain was half the dose required for motor improvement [33]. In patients with temporomandibular disorders, a single injection of BoNT/A resulted in a decrease in bite force for a shorter period, compared with a beneficial effect on pain [34].

BoNT/A has shown efficacy in treating various pains such migraine, diabetic neuropathy, trigeminal neuralgia, post-herpetic neuralgia, poststroke pain, spinal cord injury, cancer pain, pelvic pain and more. Based on the results of a pooled analysis of 2 multicenter studies evaluating migraine prophylaxis, OnabotulinumtoxinA was approved by the FDA for the prophylaxis of chronic migraine in

2010 and is now widely used worldwide [35].

Four articles describing the efficacy of botulinum toxin in diabetic neuropathy were analyzed, all of which were double-blind randomized control studies.

In a study by Yuan et al. [36] 50 U BoNT/A was injected intradermally into both feet at 12 sites. Evaluation performed at 1, 4, 8 and 12 weeks showed a significant decrease in pain on the visual analogue scale, lasting throughout all 12 weeks and peaking at 4 weeks with a score of 2.22 ± 2.24. A temporary improvement in sleep was also demonstrated at week 4 of treatment with scores of 1.72 ± 1.82.

Later, a similar study was conducted by Ghasemi M. et al., the distinguishing features of which were a 2-fold increase in the dose of botulinum toxin and its injection into only one foot. Intradermal injection of BoNT/A reduced sensitivity for electric shocks, burning, pins and needles and brushing [37]. The duration of this study was only 3 weeks due to the problems regarding patients regular follow-up.

The results of the Salehi et al. [38] study showed that the sleep quality in diabetes patients improved significantly after the BoNT/A injection in weeks 4 and 8, as well as the individuals' level of physical capacity. In the latest study [39], published in 2020, the dose was increased to 150 U, and groups injected in one and both feet were compared. Interesting that all types of pain improved significantly in both groups. However hot sensation improvement was higher when one foot was injected.

Thus, the treatment of diabetic neuropathy with botulinum toxin A is an effective method but requires further study.

In recent years, the use of botulinum toxin for the treatment of sleep bruxism has been studied. In one of these studies, after the introduction of toxin injections into the masticatory muscles, a month later, as well as 3 months later, somography was performed in the laboratory. As a result, it was found that BoNT type A can protect masticatory structures from excessive stress and thus serve as an effective treatment method [40]. A study published a year later confirmed the efficacy of low doses of the toxin in treating patients not responding to more classical therapies [41].

The effectiveness of botulinum toxin for pain control in patients with myofascial temporomandibular disorders has been evaluated in comparison with other treatments, with only botulinum toxin injections improving pain threshold values. A significant disadvantage was the decrease in EMG activity in the injected muscles [42]. In 2022, this toxin was effectively used for the treatment of androgenetic alopecia. The authors suggested that the mechanism of action of botulinum toxin in alopecia is to relax the muscles of the head, increase blood flow and inhibit the activation of Dihydrotestosterone [43]. In 2021, data were published, according to which the reduction of post-stroke spasticity with a single injection of botulinum toxin reduces the rate of contracture formation and the need for concomitant treatment [44].

Practical aspects

Two botulinum neurotoxins, types A and B, are used in clinical practice. While there are at least seven commercially available type A preparations: Botox® (Allergan, Inc., Irvine, California), Dysport® (Ipsen, Ltd., Berkshire, United Kingdom), Xeomin® (Merz Pharmaceutical, Greensboro, NC), PurTox® (Mentor Worldwide LLC, Santa Barbara, California), Neuronox® (Medy-Tox Inc., South Korea), CBTX-A (Lanzhou Institute of Biological Products, China), and CNBTX-A (Nanfeng Medical Science and Technology Development Co. Ltd., China), there is only one commercially available botulinum toxin type B MyoBloc® (Solstice Neurosciences, Inc., Louisville, Kentucky) or NeuroBloc® (Eisai Co., Ltd, United Kingdom) [45].

Numerous studies have shown the same effectiveness of Botox®, Dysport®, Xeomin®, however, there are differences in recommended doses and cost-effectiveness. Botox®:Dysport®:Xeomin® conversion ratio even to 1:3:1. While all three products have similar efficacy when dosed correctly, Dysport® injections are more economical [46]. Other commercial formulations of botulinum toxin A are relatively new products and therefore the amount of clinical data on these products is very limited in the scientific literature. For example, the Chinese drug CBTX-A, also known under the trade name Prosigne®, matches Botox® in its efficacy, duration of action, frequency and severity of adverse side effects in the treatment of blepharospasm and hemifacial spasm [47]. Comparison of drugs based on two different types of botulinum toxin, A and B, led to the following conclusions. First, side effects extend farther from the site of Botox® injection compared to equivalent doses of Myobloc®/NeuroBloc®. Second, side effects are more common with Myobloc®/NeuroBloc® injections than with Botox®, but they are usually mild to moderate and often improve with repeated use [48].

Botulinum toxin is administered intramuscularly in doses depending on the individual characteristics of the patient, among which are sex, age, and weight. Special equipment to control the administration of the drug is usually not required. The validity period can vary greatly, usually lasting about three months. In this case, it is possible to conduct additional injections to achieve repeated relief over the years. Injection resistance may develop due to the production of neutralizing antibodies. Early studies have shown that patients who develop antibodies to botulinum toxin type A may benefit from repeated injections of botulinum toxin type B. Botulinum toxin injections can lead to some side effects related to its paralytic action. With the introduction of large doses, it is possible to spread the toxin to nearby muscles, further weakening them. May occur as weakness of distant muscles or general weakness, a flu-like condition. Contraindications for the use of botulinum toxin include pregnancy and breastfeeding [49].

Future therapeutic opportunities

New botulinum toxin molecules for medical use continue to be developed. One of the promising applications of non-paralyzing botulinum toxin preparations is the development of long-acting painkiller. Work on the evaluation of the possibility of using such analgesics will allow in the future to create an effective and safe way to control chronic pain. Reengineering BoNT is able to eliminate its paralytic effects. There are various approaches aimed at manipulating the structure of the toxin: not only can they improve its safety profile, but they can also increase its effectiveness as an analgesic. Examples of such molecular approaches are SNARE tagging and SpyCatcher-SpyTag.

Protein crosslinking technology uses the self-assembly properties of SNARE proteins to form a heteromeric tetrahelix between recombinant domains. This forms an irreversible and stable peptide bridge that binds proteins into one functional unit. The BoNT/A protease and translocation domains are produced with a SNAP25 linker at one end, and a receptor-binding domain is also produced that attaches to the synaptobrevin linker. When the crosslinking peptide syntaxin is added to the reaction, the SNARE proteins self-assemble and the protease, translocation, and receptor binding domains combine to form a single, functioning toxin that enters cells and cleaves the SNARE proteins.The SpyTag/SpyCatcher technology is a method of irreversible conjugation of recombinant proteins with the formation of an isopeptide bond. It this metod the protease and translocation domains of BoNT/A are produced with a SpyCatcher protein at one end, and a receptor-binding domain is produced with SpyTag protein.

Conclusions

The burden of chronic pain is multifaceted. It is associated with a deterioration in the quality of life, a reduction in social relationships, an increase in disability, and a decrease in productivity. Most patients suffering from chronic pain are currently dissatisfied with the pain therapy they receive,

despite the existence of numerous pharmacological methods of pain control. This is due to the shortcomings of modern pharmacotherapy, namely, a short duration of action, regular use of drugs, and possible side effects. In addition, persistent pain leads to the formation of comorbid psychological disorders, the excessive use of pharmacological agents, the development of tolerance or drug dependence.

Numerous clinical reports on the use of botulinum toxin for pain control show a unique long-term reduction in pain after a single application lasting 3 to 6 months. Another advantage of using botulinum toxin is that there are no serious side effects other than those caused by its paralyzing nature. Scientific resources need to be directed towards improving the safety profile of botulinum toxin products aiming to remove muscle paralysis and thereby increasing their efficacy in reducing the duration and severity of chronic pain.

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Ботулинум токсинінің клиникалық қолданылу мысалдары: әдебиетке шолу

Аңдатпа. Ботулинум токсині (BoNT), адамзатқа белгілі ең улы заттардың бірі, өзінің ерекше әсер ету механизмі арқылы көптеген ауруларды, соның ішінде страбизмді, блефароспазмды және гемифасиальды спазмды емдеудің тиімді құралы ретінде қолданылады. BoNT ауырсыну нейропептидтерінің экзоцитозын, соның ішінде CGRP, P субстанциясы тежеу және TRPV1, NMDA, AMPA, P2X3 сияқты ауырсынумен байланысты рецепторлардың экспрессиясын модуляциялау қабілетінің арқасында ұзақ әсер ететін анальгетик ретінде арнайы қолданылды. Ботулинум токсинінің инъекциясы көптеген ауырсыну жағдайларын емдеуде тиімді: диабеттік нейропатия, созылмалы мигрень, жұлынның зақымдануы. Бұл мақалада PubMed дерекқорындағы нақты іздеу сұраулары бойынша мақалаларды талдау негізінде ботулинум токсинін клиникалық қолдану мүмкіндіктері қарастырылады. Сілтемелерді алу үшін "ботулинум токсині", "емдеу", "клиникалық қолдану", "ауырсынуды азайту" түйін сөздері қолданылды. Ботулинум токсинін клиникалық қолдану мүмкіндіктері жыл сайын кеңейіп келеді. Қазіргі уақытта А және В типті ботулинум токсинінің кем дегенде 8 коммерциялық қол жетімді препараттары белгілі, олардың ішіндегі ең танымалдары Botox, Dysport және MyoBloc/NeuroBloc болып табылады. Болашақ зерттеулер қауіпсіздік профилін жақсартуға және ботулинум токсиніне негізделген препараттардың тиімділігін арттыруға бағытталуы керек. Молекулалық реинжиниринг арқылы алынған ботулинум токсинінің жаңа түрлері оның емдік тиімділігін айтарлықтай арттырады.

Түйін сөздер: ботулинум токсині, клиникалық қолданылуы, созылмалы ауырсыну, ауырсынуды жеңілдету, анальгетиктер, мигрень, диабеттік нейропатия.

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Примеры клинического использования ботулинического токсина: обзор литературы

Аннотация. Ботулинический токсин (BoNT), являясь одним из самых токсичных веществ, известных человечеству, благодаря своему уникальному механизму действия используется в качестве эффективного средства для лечения многих заболеваний, в том числе страбизма, блефароспазма и гемифациального спазма. BoNT получил особое применение в качестве анальгетика длительного действия благодаря его способности ингибировать экзоцитоз нейропептидов боли, включая CGRP, субстанция P, и модулировать экспрессию таких рецепторов, связанных с болью, как TRPV1, NMDA, AMPA, P2X3. Инъекции ботулотоксина эффективны при лечении многих болевых состояний: диабетической невропатии, хронической мигрени, повреждениях спинного мозга. В данной статье рассматриваются возможности клинического применения ботулотоксина на основе анализа статей в базе данных PubMed по конкретным поисковым запросам. Для получения ссылок использовались ключевые слова «ботулотоксин», «лечение», «клиническое применение», «уменьшение боли». Возможности клинического применения ботулотоксина с каждым годом расширяются. В настоящее время известно не менее 8 коммерчески доступных препаратов ботулинического токсина типов А и В,

наиболее узнаваемыми из которых являются Botox, Dysport и MyoBloc/NeuroBloc. Будущие исследования должны быть направлены на улучшение профиля безопасности и повышение эффективности препаратов на основе ботулотоксина. Новые типы ботулинического токсина, полученные путем молекулярной реинжиниринга, значительно повысят его терапевтическую эффективность.

Ключевые слова: ботулотоксин, клиническое использование, хроническая боль, обезболивание, анальгетик, мигрень, диабетическая нейропатия.

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