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THE USE OF BOTULINUM TOXIN AND ITS ROLE IN PAIN MANAGEMENT- A SYSTEMATIC REVIEW

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ABSTRACT

Introduction and Purpose: For many decades, botulinum toxin has been used in various fields of medicine, from aesthetic procedures to urology and neurology. It has become a highly effective and important therapeutic tool in the hands of a qualified physician. The aim of this article is to provide an overview of current research on the use of botulinum toxin in medicine, with a particular focus on its role in the treatment of various types of pain.
Materials and Methods: A literature review was conducted using the PubMed and Google Scholar databases. Relevant keywords were used as search terms.
Conclusion: Botulinum toxin, a neurotoxin with a good safety profile, is used in numerous branches of medicine and plays an increasingly important role in the treatment of various pain conditions. This review presents the current state of knowledge on the mechanism of action and analgesic properties of botulinum toxin and highlights its promising potential in the development of new therapeutic methods.

KEYWORDS

Botulinum, Botulinum Toxin, Botulinum Toxin Type A, Migraine, Pelvic Pain, Trigeminal Neuralgia, Cluster Headache

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Introduction

Procedures using botulinum toxin are among the most commonly performed non-surgical interventions in the world. It was first approved by the US Food and Drug Administration (FDA) in 1989 as a treatment for strabismus and blepharospasm. Since then, the list of its official medical indications has expanded significantly. Currently, the FDA has approved its use in the treatment of chronic migraine, overactive bladder, muscle spasticity, cervical dystonia and hyperhidrosis [54][17][18].

Botulinum toxin is produced by the bacterium Clostridium botulinum. Once it enters a neuron, it triggers a series of biochemical reactions that result in the degradation of the SNARE complex and permanent blockage of acetylcholine release at the neuromuscular junction. The clinical effect is flaccid muscle paralysis. [6][7][8]. Due to its unique properties, botulinum toxin has become the subject of intensive research in many fields of medicine around the world. In addition to the medical indications approved by the FDA, it is also used in several'off-label' therapies — including cases where clinical benefits have been documented but there is no formal regulatory approval or standardised dosing regimens. In addition to its well-established position in the treatment of chronic migraine, botulinum toxin has also been shown to be effective in the treatment of other pain conditions, such as tension headaches, trigeminal neuralgia and pelvic pain. [18][44]. The increasingly widespread use of botulinum toxin in medicine, combined with growing international interest in it, particularly in the context of pain management, has significantly improved the quality of life of patients on a global scale.

Botulinum Toxin in Medicine: A Historical Perspective

The history of the use of botulinum toxin in medicine as a therapeutic agent is extremely interesting and multifaceted. In the past, this substance aroused fear and concern because it was associated with severe food poisoning. Over two hundred years ago, German physician and poet Justinus Kerner was the first to describe cases of botulism that occurred after consuming contaminated meat. In his works published between 1820 and 1822, he suggested the possibility of using the toxin for medicinal purposes, especially in the treatment of disorders associated with excessive muscle activity, by reducing it. [11].

However, botulinum toxin in its pure form was not identified until 1897, when Professor Emile van Ermengem, a bacteriologist at the University of Ghent, discovered it as the agent responsible for mass food

poisoning during a banquet in Belgium. [12][13]. The actual isolation and purification of the toxin was carried out by Carl Lamanna and Edward Schantz during research conducted during World War II. Its mechanism of action was later discovered thanks to the research of Burke, Snipe and Brogan.[13][14].

The ophthalmologist Alan B. Scott is considered to be the true pioneer of the use of botulinum toxin in medicine, who in 1979 administered the toxin to treat strabismus in children and adults [15][16]. However, formal approval of botulinum toxin for the treatment of strabismus and blepharospasm by the US Food and Drug Administration (FDA) did not occur until 1989, ten years later [17].

As medical science has advanced, botulinum toxin has gained a number of new therapeutic indications. Since the late 1980s, its potential in aesthetic medicine has also been recognised. In 2002, the FDA approved its use for the reduction of glabellar lines in the upper face. Currently, the list of clinically approved uses for botulinum toxin includes chronic migraine, cervical dystonia, blepharospasm, strabismus, excessive underarm sweating, overactive bladder, and spasticity, among others. [18].

Research on this neurotoxin is ongoing, and the results are very promising. Well-documented indications, confirmed by clinical trials, include focal and movement dystonia, chronic pain syndromes, bruxism, congenital clubfoot, hallux valgus, post-traumatic joint contractures, and complications associated with scleroderma [18][19][20].

Structure and Mechanism of Action

Botulinum toxin (BoNT) is produced by anaerobic bacteria of the genus *Clostridium*. It is a protein neurotoxin with a molecular weight of approximately 150 kDa, consisting of two chains: heavy (~100 kDa) and light (~50 kDa), connected by a disulphide bridge [1][2]. In its original form, the toxin remains inactive and is only activated after the disulphide bond is broken and the two chains are separated [3].

To date, seven serotypes of botulinum toxin have been identified: A, B, C, D, E, F and G. However, only serotypes A and B are used in everyday medical practice [4]. Type A is the most commonly used due to its high efficacy, while type B is mainly used in patients who have developed antibodies that neutralise BoNT/A [5].

Botulinum toxin acts on cholinergic neurons. Its action begins with the attachment of the heavy chain (HC) to the presynaptic neuron, followed by its internalisation into the synaptic vesicle via endocytosis. The acidic environment of the endosome activates the toxin, reducing the disulphide bridge and separating the light chain (LC) from the heavy chain (HC). The light chain enzymatically breaks down the SNARE protein complex, a critical component for the docking and fusion of synaptic vesicles with the neuron's membrane. This degradation prevents the release of acetylcholine (ACh) into the synaptic cleft, leading to a state of flaccid muscle paralysis.[6][7][8].

However, this paralysis is completely reversible — over time, the activity of the toxin decreases and the SNARE complex is completely restored. [9][10].

Results

Thanks to its broad spectrum of action, botulinum toxin has become recognised as a versatile therapeutic agent used in numerous areas of medicine. The following sections of this paper will provide detailed information on the conditions in which it is used, with a special focus on managing different forms of pain. This review is based on a thorough analysis of current clinical studies and the latest scientific reports.

Botulinum Toxin and Migraine

Migraine is considered one of the most disabling conditions globally, affecting up to 15% of the adult population and ranking as the 7th leading cause of disability worldwide [21]. The highest prevalence is observed in the 35–39 age group, with women being disproportionately affected [22]. Migraine is defined as a chronic neurological disorder characterized by intense, recurrent headaches accompanied by a range of neurological symptoms such as nausea, photophobia, and phonophobia [23]. This condition poses a significant challenge to modern medicine, and extensive research continues to investigate its pathophysiology and treatment strategies.

On October 15, 2010, OnabotulinumtoxinA was approved by the U.S. Food and Drug Administration (FDA) for the prophylactic treatment of chronic migraine in adults, becoming the first biologically approved drug for preventing headache episodes in patients with chronic migraine [24].

According to current research, botulinum toxin exerts its therapeutic effects by inhibiting the release of pain-related neurotransmitters, such as calcitonin gene-related peptide (CGRP) and substance P, thereby reducing the transmission of nociceptive stimuli in the central nervous system [25].

A Cochrane meta-analysis published in 2019 evaluated the effect of botulinum toxin on the duration and intensity of migraine attacks. The results showed that BoNT-A reduced the number of migraine days by an average of two days per month and was associated with a favorable safety profile [26].

Additional randomized clinical trials have demonstrated that BoNT-A reduced the frequency of migraine episodes by nearly 50% compared to control groups [27]. Treatment with botulinum toxin was generally well-tolerated by patients and led to improvements in quality of life (QoL) assessments. A major advantage of botulinum toxin type A, as demonstrated in numerous studies, is its safety. The incidence of adverse effects was low, and tolerability was significantly better than with many other pharmacological options [28].

Furthermore, a PRISMA meta-analysis showed that botulinum toxin was associated with fewer adverse effects than topiramate, a drug commonly used in migraine treatment [29]. Nevertheless, a five-year retrospective study revealed that adverse effects may occur in patients undergoing long-term BoNT-A therapy for chronic migraine. One of the most frequently reported side effects was neck pain, affecting 17.5% of the 489 patients in the study. Other reported symptoms included eyelid ptosis, temporal muscle atrophy, and lateral brow elevation. Importantly, no serious adverse events or deaths were reported [30].

In summary, botulinum toxin type A (BoNT-A) is a proven and approved treatment for chronic migraine, defined as headaches occurring on at least 15 days per month, with a minimum of 8 days meeting the criteria for migraine. This therapy not only alleviates the severity of symptoms, but also reduces the number of days with pain and the frequency of attacks. Thanks to its favourable safety profile and high tolerance, BoNT-A significantly improves patients' quality of life. In clinical practice, botulinum toxin has become an important tool in the treatment of chronic migraine, especially in people who do not respond to standard treatment or in whom the use of oral medications is contraindicated.

Efficacy of Botulinum Toxin in Non-Migraine Headaches

Currently, botulinum toxin type A is not officially approved for the treatment of headaches other than chronic migraine. However, numerous studies and clinical trials are underway to evaluate its effectiveness for other types of headaches, and its use in these situations is considered an off-label treatment.

Due to the mode of action of botulinum toxin, scientists have hypothesized that it may alleviate tension-type headaches (TTH). While the results of studies to date are mixed, much of the data indicates a reduction in pain intensity in patients, most often assessed using a VAS scale. Additionally, some participants reported a decrease in the number of headache episodes, and some noted a reduced need for pain medication.

[31][32]Due to the limited number of available studies, the lack of large randomized controlled trials, and the lack of standardized dosing regimens, the effectiveness of botulinum toxin in the treatment of TTH cannot be definitively assessed at this time. Nevertheless, the existing data are promising and suggest the need for further research in this area. Similarly encouraging results have been reported for the use of botulinum toxin in the treatment of cluster headaches. This type of headache, classified as primary trigeminal headache with an autonomic component (PAT), is characterized by exceptional severity. Cluster headaches are approximately four times more common in men, with the highest incidence observed between the ages of 20 and 40 [33][34]. The use of botulinum toxin in the treatment of cluster headaches remains experimental. However, an analysis of three prospective studies showed promising results, with patients beginning to experience improvement approximately one week after treatment. Most of them reported both a reduction in the number of pain attacks and at least a 50% decrease in pain intensity during attacks [35]. However, due to the lack of standardized dosing protocols and standardized administration schedules, it is currently impossible to clearly assess the effectiveness of botulinum toxin in the treatment of various headache types, nor to develop consistent recommendations for its use beyond migraine.

Trigeminal Neuralgia and Botulinum Toxin

Trigeminal neuralgia (TN) is a chronic disorder of the nervous system in which patients experience sudden, severe, and short-lasting attacks of pain, often compared to electric shocks. The trigeminal nerve, the largest cranial nerve, is responsible for transmitting sensory stimuli to the front of the face and head [36]. Due to the severe and paralyzing nature of the pain, trigeminal neuralgia significantly reduces the quality of life of patients, prompting researchers to search for new, more effective treatment methods. Pharmacological therapy

typically involves carbamazepine and oxcarbazepine, but there is growing evidence of the benefits of lamotrigine, gabapentin, and botulinum toxin type A (BoNT-A) as adjunctive therapy, and in some cases, even alone [37]. The first reports suggesting the effectiveness of botulinum toxin type A (BoNT-A) in the treatment of trigeminal neuralgia appeared in 2002. Initial studies showed that over 70% of patients responded positively to treatment [38]. A 2016 meta-analysis confirmed that BoNT-A not only alleviated pain intensity but also reduced the frequency of attacks in people suffering from this condition [39]. The first beneficial effects of treatment were visible as early as two weeks after injection, with the most noticeable change being a reduction in pain [40]. Although clinical observations indicate a beneficial effect of BoNT-A in people with trigeminal neuralgia, these studies were not based on uniform, standardized procedures. The lack of large-scale, randomized trials with uniform dosing regimens means that botulinum toxin has not yet gained official acceptance as a treatment for this condition [38]. Nevertheless, the available results suggest that BoNT-A treatment is effective and well-tolerated. The most frequently reported side effect was temporary facial asymmetry. Therefore, botulinum toxin seems to be a promising alternative, especially for patients who cannot benefit from traditional pharmacotherapy or surgical procedures [41].

Botulinum Toxin in Pelvic Pain

Chronic pelvic pain (CPP) is defined as persistent pain for at least 3–6 months that is unrelated to pregnancy, menstruation, or trauma. It is estimated that this problem may affect up to one-quarter of women of reproductive age, making it a significant global health challenge and requiring carefully planned treatment [42]. Chronic pelvic pain most often manifests as persistent or recurring pain that patients describe as dull, stabbing, or burning, often accompanied by tingling or numbness. Early symptoms may include painful intercourse, difficulty urinating, and difficulty with bowel movements. The exact causes of this condition are not fully understood, but a possible association with endometriosis, pelvic adhesions, chronic inflammatory conditions, irritable bowel syndrome, or pelvic floor muscle dysfunction is often suggested [43]. Due to its high prevalence and significant impact on quality of life, finding effective treatments for chronic pelvic pain (CPP) is a major research challenge worldwide. A growing number of studies indicate the potential effectiveness of botulinum toxin therapy in women with CPP. The results of a 2021 cohort study are particularly promising, with all participants reporting a reduction in pain following injection. The therapeutic effect was maintained for up to 26 weeks, after which pain intensity returned to baseline. Additionally, a 23.8% reduction in opioid use was observed among participants [44]. A randomized, placebo-controlled trial further demonstrated that botulinum toxin effectively alleviates symptoms of chronic pelvic pain, particularly dyspareunia. Women treated with BoNT-A reported a significant reduction in pain during intercourse, assessed on a VAS scale, with the mean value dropping from 66 to 22. Furthermore, participants noted an improvement in their experience of chronic pelvic pain unrelated to the menstrual cycle [45]. More detailed studies have been conducted on patients with myofascial pelvic pain (MFPP), which is often part of the presentation of chronic pelvic pain (CPP) but is often misdiagnosed in clinical practice [46]. Among patients with MFPP who did not respond to standard conservative treatment, botulinum toxin type A injections yielded significant therapeutic effects. As many as 74% of participants reported significant improvement, while only 12% reported no change. This method appears promising in terms of both efficacy and safety. Only one adverse event was reported in the study – transient fecal incontinence, which resolved within two weeks [47].

The use of botulinum toxin in the treatment of chronic pelvic pain appears to have real clinical value. Previous studies indicate its positive impact on patient well-being and comfort. However, the lack of large, multicenter studies and standardized dosing regimens means that this therapy has not yet been formally approved by the FDA. Nevertheless, due to its promising effects and potential improvement in quality of life, further research is being conducted that may enable its official inclusion in the standards of treatment in the future.

Complications

Botulinum toxin undoubtedly plays a significant role in modern medicine, but its use is associated with certain risks. Therefore, it is important to be aware of possible complications following its administration. The most commonly observed side effects include pain, swelling, and bruising at the injection site. These are usually mild, resolve spontaneously within a few days, and are due to the intramuscular route of administration [48]. The second most frequently reported complication is headache, which can persist for up to two weeks after injection [49]. Side effects can also occur if botulinum toxin is administered in an inappropriate location, for example, into a different muscle than intended. This can lead to, among other things, drooping eyelids or

eyebrows, asymmetry of the smile or facial expression, and difficulty closing the eyes [30][41][50]. Administration of botulinum toxin in the pelvic region may result in side effects such as constipation, fecal incontinence, or urinary incontinence [47]. Botulinum toxin is generally considered a relatively safe substance, and most side effects disappear completely. However, very rarely, serious complications can occur, especially when a large dose of the drug is administered intravenously. In such situations, cardiac arrhythmias, heart attack, seizures, or even anaphylactic shock are possible. [51]

Immunogenicity of Botulinum Toxin Type A

Regular use of botulinum toxin may be associated with the risk of the patient developing neutralizing antibodies (NAb) directed against this substance. This process can be exacerbated by factors such as too short intervals between treatments, high doses, the antigenic protein content of the preparation, its purification level, and the conditions in which the drug is stored. This immune reaction can result in decreased therapy effectiveness, reduced therapeutic effects, and, in extreme cases, a complete lack of response to further injections.[52]

A pooled analysis has shown that neutralizing antibodies develop in approximately 1.8% of patients receiving botulinum toxin therapy. It has been found that the longer BoNT-A treatment lasts, the more frequently these antibodies are detected. In all individuals who experienced secondary loss of treatment efficacy, the presence of neutralizing antibodies was confirmed by laboratory testing. This problem was primarily observed in individuals treated for dystonia, spasticity, and urological conditions, whereas it was not observed in patients undergoing hyperhidrosis or aesthetic treatments.[53] In summary, the rate of antibody production against botulinum toxin type A is relatively low; however, in certain situations, an immune reaction may result in temporary or permanent exclusion of the patient from further therapy. Therefore, further research and the development of unified guidelines for optimal management of immunoresistance are necessary.

Conclusions

Botulinum toxin plays a significant role in modern medicine, and its range of applications has been steadily expanding for over five decades. It is the subject of intensive scientific research and has undoubtedly revolutionized therapeutic approaches in numerous fields, such as dermatology, urology, and neurology. Its therapeutic potential is particularly evident in the treatment of various pain syndromes. To date, only chronic migraine has been officially approved as an indication for botulinum toxin treatment. However, a growing body of scientific evidence confirms its effectiveness in relieving pain associated with other conditions, such as pelvic pain, neuropathic pain, trigeminal neuralgia, and tension-type headaches.

Despite promising results, the use of botulinum toxin in these areas is still off-label and requires in-depth research. Currently, there are no uniform therapeutic guidelines, precisely established doses, or large-scale, randomized clinical trials encompassing diverse patient groups. However, the available results are promising and may lay the foundation for expanding the medical indications for this substance in the future. It's also crucial to be aware of possible side effects resulting from its use. Although botulinum toxin is considered a relatively safe preparation, it is a potent drug that should be administered with extreme caution and in the hands of an experienced physician.

Author's contribution

Conceptualization, Małgorzata Słaboń, Karol Stępniak, Wojciech Gąska; methodology, Daria Madycka, Kinga Wnuczek, Wiktor Telega; software, Jędrzej Kęsik, Aleksandra Kaźmierczyk; check, Weronika Skrzypek, Jędrzej Kęsik, Małgorzata Słaboń, Karol Stępniak, Wojciech Gąska, Daria Madycka; formal analysis, Kinga Wnuczek, Wiktor Telega, Weronika Skrzypek; investigation, Małgorzata Słaboń, Karol Stępniak, Wojciech Gąska, Aleksandra Kaźmierczyk; resources, Małgorzata Słaboń, Joanna Wrona, Daria Madycka, Kinga Wnuczek, Wiktor Telega; data curation, Małgorzata Słaboń, Jędrzej Kęsik, Aleksandra Kaźmierczyk; writing - rough preparation, Małgorzata Słaboń, Karol Stępniak, Wojciech Gąska, Wiktor Telega; writing - review and editing, Małgorzata Słaboń; visualization, Joanna Wrona, Daria Madycka, Kinga Wnuczek, Wiktor Telega, Weronika Skrzypek; supervision, Małgorzata Słaboń, Jędrzej Kęsik, Aleksandra Kaźmierczyk; project administration, Małgorzata Słaboń;

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