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The impact of botulinum toxin on the health, physical condition, and mental well-being of individuals suffering from chronic migraines.

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ABSTRACT

Introduction and purpose: Migraines are one of the most common neurological conditions in the world. They are characterized by recurring, intense headaches, often on one side of the head, which may be accompanied by symptoms such as nausea, vomiting, and sensitivity to light and sound. Migraines affect overall well-being and are an indicator of health, as well as potentially causing difficulties in normal functioning. One of the most effective methods of treating migraines in recent times has become botulinum toxin. This literature review will discuss how botulinum toxin affects the body and the course of treatment for chronic migraines.

Material and methods: The literature was conducted using "Pub Med" and "Google Scholar" databases with the keywords „botulinum toxin", „botox", „migraine", „botulinum toxin type A".

Brief description of the state of knowledge: Treatment of chronic migraines with type A botulinum toxin preparations was a breakthrough discovery. This medication demonstrates high effectiveness and better tolerance compared to other preparations used in the treatment of chronic migraines.

Results and conclusions: Type A botulinum toxin has emerged as a versatile therapeutic tool with approved indications for treating chronic migraines and various other medical conditions. Despite its widespread application, gaps in research persist, particularly concerning its use during pregnancy, lactation, and among individuals under 18 years old. Further comprehensive studies in these demographics hold the potential to revolutionize chronic migraine treatment approaches. The administration method of botulinum toxin, exemplified by the Botox (Allergan) preparation, is meticulously defined and substantiated by extensive research validating its efficacy over the years.

Keywords: botulinum toxin; botox; migraine; botulinum toxin type A

INTRODUCTION

Migraine is a pervasive condition affecting nearly all of us, stands as one of the foremost culprits behind headaches on a global scale. Statistical insights reveal its prevalence in up to 12% of the populace, with a notable predilection towards women [1-3]. The enduring torment of chronic migraine pain can wield profound disruptions to daily life, heralding a cascade of health ramifications spanning both psychological and physical realms [1,2].

Botulinum toxin, long entwined with the specter of botulism-induced toxicity, has transcended its sinister associations to emerge as a versatile therapeutic agent. While botulinum toxin type A has carved a niche in the domain of aesthetic medicine, its profound impact extends to the realm of chronic migraine treatment and a myriad of other medical conditions [4-6]. At the heart of its therapeutic efficacy lies its intricate mechanism of action: BoNT/A intervenes at the neuromuscular junction, orchestrating paralysis of muscle contraction by interdicting the release of acetylcholine. Concurrently, it curtails the liberation of pain mediators, thus conferring analgesic relief [7-12].

A milestone moment arrived in 2010 with the registration of Botox® (Allergan) for chronic migraine therapy. Based on extensive testing and clinical research, a standardized protocol was established for administering this type of botulinum toxin to alleviate chronic migraines [4, 13].

Despite the widespread adoption of botox, therapeutic hurdles persist, particularly evident in the management of pregnant and postpartum women, as well as in pediatric cases [4]. Within the confines of this discourse, the aim is to elucidate the pivotal role of botulinum toxin in chronic migraine therapy, predicated upon a meticulous appraisal of extant literature.

EPIDEMIOLOGY OF MIGRAINES

Migraine is one of the most prevalent causes of headaches worldwide. It stands out as a leading cause of poor health and indicators of discomfort among the population [1, 2].

In the epidemiology of migraines, genetic factors play a significant role. It is estimated that the risk of migraines among relatives is about three times higher than in individuals without a family history of migraines. Nevertheless, genetics is not the sole cause of migraines; the combination of genetic and environmental factors plays a crucial role [14].

To understand how prevalent migraines are among the population, one must refer to statistical data, which indicates that migraines affect 12% of the population, including 17% of women and 6% of men within a year [3].

In literature, it is often stated that no other infectious or non-infectious disease is responsible for a greater number of lost healthy years of life in women, even though it does not directly cause premature death itself.

In 2019, headache disorders ranked 14th among the causes of DALYs (Disability-Adjusted Life Years) [15].

The International Headache Society has categorized migraines into subtypes. These include migraine without aura, migraine with aura, and chronic migraine [16].

The particular significance of using botulinum toxin can be attributed to conditions occurring with chronic migraine, hence we should examine it more closely. According to the International Headache Society chronic migraine is a headache that occurs 15 or more days per month for over three months, with features of migraine on at least eight or more days per month [16, 17].

Botulinum neurotoxin has been widely employed in the treatment of conditions characterized by heightened muscle tension. Recent scientific findings further validate its analgesic properties which explains its application in certain cases of chronic migraine [13].

MECHANISM OF ACTION

Botulinum toxin type A (BoNT/A) is a substance primarily known for its use in aesthetic medicine procedures. However, it has wide-ranging applications beyond this field [14].

According to the product characteristics of the medicinal product Botox ® (Allergan), the indications for its use include selected focal spasticity disorders, blepharospasm, idiopathic cervical dystonia, selected urinary bladder dysfunction disorders, skin disorders and its appendages, including hyperhidrosis, as well as the aforementioned chronic migraine [4-6].

To fully understand how botulinum toxin type A can be useful in treating chronic migraines, one must examine its mechanism of action.

Botulinum neurotoxin (BoNT) is synthesized by various strains of gram-positive bacteria, primarily Clostridium botulinum, alongside other species including C. butyricum, C. baratii, and C. argentinense [7]. Structurally, botulinum toxin is a protein complex characterized by two distinct components - a potent neurotoxic element and auxiliary proteins essential for its function. This toxin manifests in seven serological types, denoted as types A through G [7,8]. However, it's worth noting that only types A and B have demonstrated clinical efficacy [8]. In the context of migraine treatment within Poland, the approved medication is Botox® by Allergan, formulated with 200 units of type A toxin, each possessing a molecular weight of 900

kD [4,8]. This preparation is packaged in vials, facilitating the preparation of injectable solutions optimized for therapeutic use.

When administered intramuscularly, botulinum toxin type A acts at the neuromuscular junction by inhibiting the protein SNAP-25, which is essential for the release of the neurotransmitter acetylcholine from the presynaptic membrane. This inhibition prevents muscle contraction [7, 9, 10]. The mechanism by which botulinum toxin contributes to the analgesic effect in migraine treatment is complex and not fully understood. There are many theories explaining the pain-relieving action of preparations containing botulinum toxin. It is suggested that the toxin reduces transmission in the sympathetic nervous system. Additionally, it directly inhibits reactions leading to migraine formation by reducing the release of pain mediators and inflammatory substances within the trigeminal nerve (such as glutamic acid, substance P, CGRP and expression of the nociceptive sensitizing receptor TRPV) [8, 11, 12].

The latest studies have shown that botulinum toxin type A significantly reduces CGRP, as demonstrated by in vitro experiments on animals and in individuals using therapeutic preparations of botulinum toxin in the treatment of chronic migraines. In the group of patients treated with botulinum toxin preparations and responding to treatment, the level of CGRP in the serum between attacks decreased [13].

The discovery of these capabilities of botulinum toxin has led to a breakthrough in the treatment of migraines and other types of headaches. In order to understand how innovative this discovery was, attempts were made to compare the pain-relieving effect of botulinum toxin with oral pain medications.In light of this, studies were conducted comparing the efficacy of topiramate and BoNT/A. They demonstrated comparable effectiveness of both preparations, while botulinum toxin type A resulted in significantly fewer adverse effects, thus proving its better tolerance [18, 19].

While numerous authors extol the advantageous outcomes of botulinum toxin in managing chronic migraines, the body of research remains inadequate to definitively ascertain the effectiveness and safety of these formulations in addressing episodic migraines [13].

The case of a 23-year-old patient described in 2024 appears to be intriguing, as she suffered from an arteriovenous malformation causing secondary migraines that significantly impacted her life. The patient did not respond to oral treatments, so a decision was made to administer 155 IU of Botox to reduce migraine symptoms. After 7 days from the injection, the headache completely disappeared, and her quality of life markedly improved. The patient

remains in stable condition under neurological control to this day. This case demonstrates that botulinum toxin is not only suitable for treating primary migraines but also secondary ones [20].

DIAGNOSIS AND TREATMENT

To qualify a patient for treatment with preparations containing botulinum toxin in this instance, it is imperative to initially diagnose chronic migraine [4, 22]. The diagnostic process presents notable challenges, necessitating a comprehensive patient history encompassing the severity and frequency of headaches over a defined timeframe, alongside supplementary evaluations such as imaging studies and neurological consultations. The primary objective of these additional assessments is to rule out potential differential diagnoses [22, 23].

The diagnostic criteria for chronic migraine (according to the International Classification of Headache Disorders ICHD-3) are as follows:

A. Headaches (tension-type or migraine) occurring on 15 or more days per month, for 3 months.
B. There have been at least 5 migraine attacks with or without aura (usually migraine attacks do not have an accompanying aura).
C. On 8 or more days per month, for 3 months:
    - the pain met the criteria for migraine with or without aura; and/or
    - the patient considers the symptoms to be migraine pain, and treatment with triptans or ergotamines was effective.
D. No other diagnosis explains the symptoms better [23].

Botulinum toxin was registered for the treatment of chronic migraines in 2010, a decision supported by multiple studies and the development of a universal injection protocol deemed safe for the majority of patients [4, 13].

According to the summary of product characteristics for Botox ® (Allergan), the pharmaceutical form of the drug is a white powder for solution for injection. Immediately before administration, 2 ml of 0.9% sodium chloride solution in the form of an injectable solution is added to the vial containing 100 units of Botox ® (Allergan) preparation. Then, the prepared solution should be gently mixed without shaking to prevent foaming.To complete one full treatment cycle for chronic migraine, 2 vials of the medication are needed. The solution obtained after dilution is drawn into 1ml syringes, resulting in 4 syringes of medicinal product with a total of 200 units. After dilution, the preparation should be stored at a temperature between 2 to 8 degrees Celsius. In such an environment, it remains stable for 24 hours. [4, 8].

Due to insufficient research, botulinum toxin treatment for chronic migraine is not used during pregnancy and lactation. The effect of botulinum toxin on fertility in reproductive-age women and men is also debatable. Studies conducted on rats have shown a decrease in fertility. However, there is not enough research within the human population to conclude that Botox (Allergan) affects fertility [4, 24, 25].

There is also insufficient research on the population under 18 years of age to determine the therapeutic effect of botulinum toxin in the treatment of migraines.

The main contraindications to treatment with type A botulinum toxin preparations include hypersensitivity to any component of the solution, myasthenia gravis, Lambert-Eaton syndrome, any disorders of neuromuscular transmission, and infection at the injection site [4].

For the purposes of the PREEMPT clinical trial, a protocol for administering Botox ® in the therapy of chronic migraines was developed [26]. It is recommended to use diluted preparation in a total quantity ranging from 155 to 195 units in the treatment of chronic migraines. The product is administered intramuscularly in 7 regions (31-39 injection points with 5 units each).

Dosage of Botox ® in the treatment of chronic migraine:

Frontalis: 20 units (4 injection points)

Corrugator supercilii: 10 units (2 injection points)

Procerus: 5 units (1injection point)- it should be administered along the midline of the muscle

Occipitalis: 30 units (6 injection points) to 40 units (to 8 injection points)

Temporalis: 40 units (8 injection points) to 50 units (to 10 injection points)

Trapezius: 30 units (6 injection points) to 50 units (to 10 injection points)

Paraspinal muse group: 20 units (4 injection points)

When administering the medicinal product, it is important to follow the principle:

1 injection unit = 0.1 ml = 5 units.

We treat all muscles symmetrically except for the Procerus. There is also the possibility of additional injections in case of significant pain. In this case, injections are administered symmetrically or not into the occipitalis, temporalis, and trapezius muscles, so that the maximum number of units does not exceed 195 [4, 8, 26].

Botox ® therapy in the treatment of chronic migraine should be repeated every 12 weeks [9]. The main question for patients eligible for botulinum toxin injection in the treatment of chronic migraines is "Is such treatment effective? The answer to this question is only one: „Yes”.

Conducted meta-analysis has proven that botulinum toxin injections, compared to placebo, significantly improved the quality of life of patients with chronic migraines after 3 months of therapy [27].

Although there are still too few studies in the population under 18 years of age, a study was conducted among teenagers suffering from chronic migraines. These studies also demonstrated the effectiveness of botulinum toxin preparations. Adverse effects among this group occurred in 4%, consisting of neck pain and headache after injection [28].

Medications often compared to botulinum toxin due to a similar mechanism of action in the treatment of chronic migraines include anti-CGRP antibodies. Extensive studies have demonstrated that both substances exhibit a favorable safety profile, with minimal side effects reported. In the case of botulinum toxin, adverse effects such as eyelid drooping, muscle weakness, and neck pain may occur, while anti-CGRP antibodies have been associated with symptoms such as constipation and upper respiratory tract infections. Interestingly, combining these therapeutic approaches has shown potential to enhance treatment outcomes. However, it's worth noting that despite the promising results, the financial aspect favors the use of botulinum toxin due to its comparatively lower cost [29].

DISCUSSION

Despite the registered use of botulinum toxin for the treatment of chronic migraines, ongoing research endeavors continue to explore its potential applications in addressing various other pain conditions.

Of particular significance is the scrutiny given to studies involving the pediatric demographic. There exists a wealth of evidence suggesting that botulinum toxin may hold promise for future use in treating chronic migraines among individuals under 18 years of age. However, as of the present day, a dearth of comprehensive research impedes its formal approval for this age group [28, 30].

Another significant challenge in utilizing botulinum toxin for migraine management lies in its therapeutic administration during pregnancy. The safety profile and fetal repercussions of toxin exposure remain incompletely elucidated. Nonetheless, emerging evidence indicates that botulinum toxin administration does not elevate the risk of fetal abnormalities [31].

The undeniable efficacy of botulinum toxin in alleviating chronic migraines among the adult population lacking risk factors is readily discernible, bolstered by a plethora of recent empirical investigations [4, 27].

Evaluating the extensive volume of research conducted on botulinum toxin in recent years, it becomes evident that its complete therapeutic potential and breadth of application remain shrouded in ambiguity. A meticulous comprehension of its physiological mechanisms holds the potential to catalyze a paradigm shift in the landscape of medical practice

CONCLUSION

Migraines are a big health problem worldwide, affecting a lot of people, especially women. They cause intense and long-lasting headaches that really disrupt daily life, both mentally and physically.

Botulinum toxin used to be known for being really toxic and causing botulism. But now, it's been transformed into a versatile treatment. It's not just used for making people look better anymore; it's also used to treat chronic migraines and other medical problems. It works by stopping muscles from moving by blocking a chemical called acetylcholine. This not only helps with muscle problems but also reduces pain.

A big moment in 2010 was when Botox® got approved for treating chronic migraines after lots of testing. But there are still challenges, especially in certain groups like pregnant women, new moms, and kids. Even so, research is ongoing to see how else botulinum toxin can help, especially in treating chronic migraines in kids and making sure it's safe for pregnant women.

The extensive volume of research conducted on botulinum toxin underscores its multifaceted therapeutic potential and the need for a nuanced understanding of its mechanisms. While its efficacy in chronic migraine treatment is well-documented, ongoing investigations seek to broaden its therapeutic horizons and elucidate its safety profile comprehensively. In doing so, botulinum toxin holds the promise of catalyzing transformative advancements in medical practice, revolutionizing the landscape of pain management and beyond.

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Author's contribution: JŚ

Conceptualization: JŚ

Methodology: AP;

Software: EKC;

Check: EJ, EHM and IS;

Formal analysis: MG and AA;

Investigation: JŚ;

Resources: JŚ;

Data curation: EHM and KB;

Writing - rough preparation: JŚ

Writing - review and editing: KK and AA

Visualization: JŚ;

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