POLISH HYPERBARIC RESEARCH 4(85)2023
Journal of Polish Hyperbaric Medicine and Technology Society

THE APPLICATION OF BOTULINUM TOXIN IN THE PROPHYLACTIC TREATMENT OF MIGRAINE

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ABSTRACT

Introduction
Migraine is a common disorder that affects about 2% of the general population, with a prevalence of 7% in men, 24% in women and 4% in children. Migraine is the fourth most disabling condition among women and the seventh most disabling worldwide. It is characterized by paroxysmal, throbbing headaches, often unilateral, accompanied by hypersensitivity to noise, light, nausea and vomiting. Migraine is divided into episodic and chronic, with chronic meaning headache for at least 15 days a month for more than 3 months, with 8 migraine days. Treatment includes non-pharmacological and pharmacological methods, but often ineffective and fraught with side effects. Chronic migraine can lead to significant disability.
Material and methods
The purpose of this article is to discuss the treatment of migraine with botulinum toxin. Information was collected from the English-language databases Google Scholar, Scopus and PubMed.
Results
Onabotulinum toxin A, approved for the treatment of migraine, works by blocking acetylcholine release at the synapse level, leading to reversible flaccid paralysis and blocking neurotransmitters such as CGRP. Injection sites include peri-cranial and neck muscles, allowing the toxin to be transported to the meninges and trigeminal ganglion. In recent years, injections near the cranial sutures have been preferred. BTX-A therapy has shown efficacy in reducing the frequency and severity of migraine pain, with fewer side effects compared to topiramate. Side effects, such as hematoma or ptosis, are rare and their frequency decreases with subsequent sessions. The cost of migraine treatment is high, but botulinum toxin reduces headache days and is cost-effective.
Keywords: Migraine, botulinum toxin, treatment.

ARTICLE INFO

PolHypRes 2024 Vol. 85 Issue 4 pp.63 – 72
ISSN: 1734-7009 **eISSN:** 2084-0535
DOI: 10.2478/phr-2023-0022
Pages: 10, figures: 0, tables: 0
page www of the periodical: www.phr.net.pl

Publisher
Polish Hyperbaric Medicine and Technology Society

Original article

Submission date: 14.08.2023 r.
Acceptance for print: 13.09.2023 r.

INTRODUCTION

Migraine is a common disease that affects about 2% of the general population. Its prevalence is about 7% in men, about 24% in women and about 4% in children. The World Health Organization's Global Burden of Disease Study 2010 found that migraine was the fourth most disabling condition among women and the seventh most disabling condition worldwide. It primarily affects young adults, as in an overwhelming number of cases (90%) the first migraine attack occurs before the age of 40 [1].

Migraine is defined as a paroxysmal, throbbing headache that may be accompanied by hypersensitivity to noise, odors and light, nausea and vomiting. The pain is mainly localized unilaterally of moderate to severe intensity, and intensifies during routine physical activity and strong emotions. Migraine can be divided according to the presence or absence of an aura, and according to the duration of symptoms into episodic or chronic. Chronic migraine is defined by the International Headache Society (IHS) as "headache for at least 15 days per month, for more than 3 months, and 8 of these days must be a migraine headache or relieved by a triptan or ergot derivative and without drug abuse [2].

Treatment of both forms of migraines focuses on treating acute attacks and preventing them. Non-pharmacological and pharmacological treatments can be distinguished. Non-pharmacological treatment can include lying in a dark room, cold compresses or pressure on painful areas, and avoiding migraine triggers. Pharmacological treatment, on the other hand, uses triptans, nasal sprays or dihydroergotamine injections, neuroleptics, nonsteroidal anti-inflammatory drugs and corticosteroids. However, the use of these preparations is not very effective, and significant side effects of these therapies can often be noted. Some patients who abuse these drugs may develop a secondary headache otherwise known as a rebound headache. This can result in more frequent migraine episodes and their severity. Migraine, if not treated effectively, can lead to significant disability. The main goals of migraine treatment include relieving pain, reducing the frequency of headaches and preventing progression to chronic migraine. More than 40 drug therapies are available worldwide, but to date only five agents have been approved by the U.S. Food and Drug Administration (FDA) for the prevention of migraine attacks. These are the beta-adrenergic receptor blockers, propranolol and thymolol, and the anticonvulsants sodium valproate and topiramate [3].

In addition, the only therapies approved for the prevention of migraine attacks are botulinum toxin A (BoNT-A), and monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway [3].

OBJECTIVE

The purpose of this article is to discuss an overview of the treatment of migraines with botulinum toxin, including useful clinical information. This can serve as a guide to the use of botulinum toxin in the prophylactic treatment of migraine, including injection sites and doses, approved indications for use, reported adverse events and impact on social problems.

METHOD

The information was gathered from a review of English-language items in databases: Google Scholar, Scopus and Pubmed. Search keywords included: migraine, botulinum toxin and treatment.

DISCUSSION

THE MECHANISM OF BOTULIN TOXIN

Migraine pain initiation takes place in the periphery. C-fiber nociceptors and A-delta pain fibers are activated, followed by sensory neurons of the trigeminal complex in the brainstem [4]. Through activation and release of vasoactive and pro-inflammatory neuropeptides/neurotransmitters, nociceptive neurons innervating the dura mater become active. Inflammatory mediators such as bradykinin, histamine, serotonin, prostaglandin E2 and interleukins 1, 6 and 8, as well as tumor necrosis factor alpha, are released. This process is made possible by CGRP, which plays a key role in migraine chronification. Therefore, the goal of botulinum toxin trapping is to interrupt the release of CGRP and other neurotransmitters [5].

The form of toxin that has been approved for the treatment of migraine is onabotulinum toxin A. The mechanism of action is to block the release of the presynaptic neurotransmitter acetylcholine at the level of the synapse at the neuromuscular junction. As a result, reversible flaccid paralysis occurs. In addition, the release of neuropeptides, inflammatory peptides and CGRP is blocked, which shows an important therapeutic role in this condition. This is made possible by blocking the SNARE complex, which is responsible for endocytosis and transmission at the synaptic junction of neurotransmitters [5].

PLACE OF DRUG ADMINISTRATION

The most common sites accepted by regulatory authorities and used in the last 10 years of toxin injections are the periocranial and neck muscles. With this location, retrograde transport through the cranial sutures to the meninges, trigeminal ganglion and occipital nerves is possible. This is made possible by collaterals passing through the cranial bones into the extracranial tissue to innervate the periosteum and extracranial muscles [6].

Recent years have shown a trend toward injecting the toxin into the muscles of the temporal region >45 mm above the zygomatic arch. However, recent studies support greater efficacy of the therapy if the injection sites are located near the cranial sutures. In addition, this strategy is less invasive (fewer injections) and less costly compared to the PREEMPT strategy used [4].

A REVIEW OF STUDIES

Comparing the results of different studies is difficult due to their different research designs and populations. Many studies have been conducted on patients with headaches related to medication abuse, but not necessarily chronic migraine. Based on a review of migraine pain management studies, it has been shown

that most patients with chronic migraine abuse medications for acute headache. Many patients and doctors are reluctant to begin discontinuing medications, fearing acute withdrawal symptoms. In a study involving patients with drug abuse, 60% of whom met criteria for chronic migraine, acute drug withdrawal resulted in a reduction in the average monthly number of migraine days and a return to episodic migraine [7].

The PREEMPT study excluded patients with daily headaches and/or comorbid depression because they are more resistant to treatment. In contrast, the Aurora et al.,2019 study included such patients because, in clinical practice, daily headaches and comorbid depression are common features of patients with chronic migraine. The exclusion of patients with daily headaches and/or comorbid depression may have contributed to the higher response rate to BTX-A, but also placebo. In fact, the response rate to BTX-A in the PREEMPT trials was extremely high, as highlighted in authoritative reports [8].

Comparison of recent studies testing anti-CGRP antibodies in chronic migraine is similarly complicated by significant differences in study design, inclusion and exclusion criteria. The placebo response rates for the primary endpoints in these trials were significantly lower compared to the PREEMPT trials. Also of note here is the significantly higher cost associated with anti-CGRP therapy [9].

Understanding the patients' perspective is an extremely important part of clinical practice and influences the final therapeutic decision. Some patients have been shown to respond in the second or third cycle of treatment with BTX-A, demonstrating the need to continue treatment, even if patients do not initially respond. Better communication with patients about these increasing benefits over time may be helpful to encourage adherence beyond the first few treatments until a therapeutic effect is seen [9].

The FORWARD trial reported a comparable therapeutic profile of onabotulinumtoxinA and topiramate with fewer adverse events with onabotulinumtoxinA. Attention is drawn to the efficacy of BTX-A demonstrated with its safety profile and reduced healthcare utilization [10].

The results of the COMPEL study indicate that the incidence of side effects associated with BTX-A treatment significantly decreased with repeated administration of the drug. In addition, choosing this therapy for the treatment of chronic migraine has a positive impact on the management of chronic comorbidities such as sleep, fatigue and anxiety [11].

SIDE EFFECTS

Regarding safety, the study showed that treatment-related side effects were significantly increased with BTX-A compared to the placebo trial. These differences remained significant considering specific complications such as headache, injection site pain, musculoskeletal stiffness, myalgia, neck pain, paresthesias and muscle weakness [12]. Considering the intensity of side effects, BTX-A has been shown to increase treatment-related side effects, but the types of events were mild and short-lived [13]. A frequently reported problem related to the administration of the drug itself was the occurrence of a small hematoma at the injection site. Additionally, a small percentage of subjects reported ptosis occurring as a result of the drug administration. It should be noted that these side effects occurred just as frequently with BTX-A or placebo administration [7]. Other long-term real-world studies have found migraine or worsening of migraine and blurred vision among the adverse events associated with OnaBoNt-A use. However, it should be noted that these were rare adverse events, and in patients continuing injections, their incidence decreased in subsequent treatment sessions, showing a satisfactory therapeutic effect [14].To date, onabotulinumtoxinA is the only prophylactic treatment for chronic migraine that has long-term real-world safety data reporting treatment-related adverse events lasting up to 3 years [15].

A REVIEW OF DRUG THERAPIES

Prophylactic treatment of migraine involves taking daily medications designed to reduce the number of headache attacks. The most common medications are cardiovascular drugs such as propranolol or flunarizine, antiepileptic drugs such as valproic acid or topiramate, and antidepressants such as amitriptyline. More recently, a safe treatment for chronic migraine has been botulinum toxin. Comparing the above-mentioned drugs, botulinum toxin A had a more significant effect on reducing headache severity and seizure frequency, but not on dizziness frequency, than the other substances [16]. Narrowing the comparisons to only botulinum toxin A and topiramate, botulinum toxin had significantly greater clinical utility than topiramate, due to more effective treatment, fewer side effects [17], reduced headache severity and depression, and improved work performance and daily functioning [18].

COSTS OF THERAPY

Chronic migraine treatment is associated with a significant economic burden. It generates not only high costs related to medication, but also to hospitalization and medical visits. In addition, the severe headache accompanying migraine has a negative impact on private and professional life, as it causes absenteeism from work and thus loss of wages. A survey of patients from Norway and Sweden noted a clear correlation between reduced quality of life and increased costs as monthly headache days increased. At the same time, botulinum toxin has been shown to markedly reduce the number of headache days and is a cost-effective treatment for chronic migraine [19], as well as reducing healthcare resource utilization and associated costs [20] .

PREGNANCY

As for the effect of botulinum toxin on pregnancy, it is not fully understood. In 2020, a study was presented saying that over a 9-year period, out of 32 women treated with botulinum toxin during pregnancy, only one had a miscarriage. The remaining patients gave birth to healthy babies at term, with normal birth weight and no birth defects [21].

SUMMARY

Migraine oscillates among the 10 most disabling conditions worldwide and mainly affects young adults. The definition indicates that it manifests itself as

a paroxysmal, throbbing headache that may be accompanied by nausea, vomiting or hypersensitivity to noise, smells and light. It is divided according to the duration of symptoms into episodic migraine lu chronic migraine, or migraine with or without aura. It is important to note from the IHS that chronic migraine is a headache occurring at least 15 days a month, for more than 3 months, and 8 of these days must be a migraine headache or relieved by pharmacological or overuse medication. It is important to remember that migraine treatment consists of treating acute attacks and preventing them from occurring. Current preparations are not very effective and are associated with numerous side effects of therapy. Moreover, overuse of medications designed to treat migraine can be associated with the occurrence of a secondary headache known as a rebound headache. In contrast, migraine untreated or treated ineffectively can lead to significant disability. Currently, of dozens of drug therapies, only five agents have been approved by the FDA for seizure prevention - the beta-adrenergic receptor blockers, propranolol and thymolol, antidepressants such as amitriptyline, and the anticonvulsants sodium valproate and topiramate.

The available form of the toxin that has been approved for the treatment of migraine is onabotulinum toxin A. By blocking the release of the presynaptic neurotransmitter acetylcholine at the level of the synapse, it is possible to reverse the flaccid paralysis caused by this substance. Observation of 10 years of toxin injection supervised by regulatory authorities has accepted the injection sites - peri-temporal muscles and neck muscles. This location provides retrograde transport through the cranial sutures to the meninges, spinal ganglia and occipital nerves. In recent years, botulism toxin has been most commonly injected into the muscles of the temporal region, but recent studies have shown greater efficacy of therapy with injection into the cranial suture area. It is important to note that some patients respond in the second or third cycle of treatment with BTX-A, demonstrating the need to continue treatment, even if patients do not initially respond. In addition, the incidence of side effects associated with BTX-A treatment decreases significantly with repeated administration of the drug. Botulinum toxin therapy has a positive effect on the treatment of chronic comorbidities such as sleep, fatigue and anxiety.

Compared with the most commonly taken migraine medications, botulinum toxin A had a more significant effect on reducing headache severity and seizure frequency, but not on dizziness frequency, than the other substances. Botulinum toxin had significantly greater clinical utility than topiramate. Despite a number of advantages of botulinum toxin therapy, it also has adverse effects due to the way the drug is administered - hematoma or ptosis. It should be noted that these were rare side effects, and in patients who continued injections, their incidence decreased in subsequent treatment sessions, showing a satisfactory therapeutic effect.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no potential conflicts of interest.

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