USE OF BOTULINUM TOXIN TYPE A IN THE TREATMENT OF MIGRAINE

Maykon Hayak Pereira Lopes[1]

Abstract: Patients with migraine often experience impacts on their personal, social, and professional lives. The disease not only impacts the individual's quality of life but also results in costs for the healthcare system and society. Despite the impact on quality of life and the costs generated for society, the disease remains underestimated, with old, nonspecific treatments of moderate efficacy and frequent adverse effects, which limits patient adherence (NACAZUME, 2019). Recently, the administration of botulinum toxin type A (BTA) has been studied as an alternative to reduce long-term adverse effects observed with other prophylactic agents (PIOVESAN et al, 2017). Therefore, the objective of this study is to analyze the efficacy of migraine treatment with BTA. To this end, a systematic review of the literature on the use of BTA in migraine prophylaxis was conducted. Patients treated with botulinum toxin type A were observed to have significantly fewer migraine attacks per month, reduced severity, fewer days using acute medications, and a reduced incidence of migraine-associated vomiting.

Keywords: Botulinum toxin type A, migraine, pain.

INTRODUCTION

Migraine is a primary neurological disorder, in which episodes of debilitating headache are accompanied by sensory changes, which can occur episodic or chronically. Migraine attacks are disabling and limiting, causing a great impact on the lives of people who suffer from the disease.

1 Anesthesiologist certified by the Brazilian Society of Anesthesiology, he graduated in Medicine from the University Center of Espírito Santo (UNESC) and completed a Medical Residency in Anesthesiology. He also works as a Medical Residency Teacher in Anesthesiology at HMSJ.

Patients who have migraine often experience impacts on their personal, social, and professional lives. The disease reflects not only on the individual's quality of life, but also results in costs for the health system and society, both direct and indirect (NACAZUME, 2019). It is estimated that the economic impact of migraine in Brazil can add up to 23.3 billion reais annually with indirect costs alone (OLIVEIRA et al, 2019).

Despite the impact on quality of life and the costs generated for society, the disease remains underestimated, with old, non-specific, medium-effective treatments, with frequent adverse effects, which limits patient adherence (NACAZUME, 2019). Recently, the administration of botulinum toxin type A (TBA) has been studied as an alternative to reduce long-term adverse effects, which are observed with other prophylactic agents (PIOVESAN et al, 2017). It is believed that its mechanism of action consists of blocking the release of neurotransmitters associated with the origin of pain and consequent action of the central nervous system to inhibit and reverse the central sensitization existing in chronic migraine.

Superior tolerability and efficacy have been demonstrated in various migraine outcomes in many controlled trials and real-life studies. BTA has been shown to be a safe and effective treatment for chronic migraine and possibly high-frequency episodic migraine (YUAN et al, 2020). Adverse effects are rare, transient, and mild, the most frequent being: muscle weakness in the neck and shoulders, post-application headache, facial asymmetries, and pain at the injection site. When compared to other drugs used in the treatment of migraine, the toxin proved to be equivalent in efficacy and promoted better tolerability and adherence. In addition, it demonstrates a prolonged action in the body, and its results can be maintained for a few months (NACAZUME, 2019).

METHODOLOGY

This article is a systematic review of the literature on the use of botulinum toxin type A in migraine prophylaxis. The review is based on articles available in databases such as PubMed, Bvsalud

and SciELO, using specific keywords. The included studies were published in Portuguese or English, and followed specific inclusion and exclusion criteria. The review process included five steps: defining objectives, identifying relevant studies, selecting studies, mapping data, and interpreting results.

THEORETICAL FRAMEWORK

The initial idea for the use of Botulinum in migraine was after observations by Binder WJ, who noticed a reduction in migraine pain symptoms in patients who received Botox® injections in the head and neck muscles during cosmetic procedures. In 2000, the results of an open-label, uncontrolled study conducted by Binder that demonstrated the efficacy and safety of Botox® as a therapeutic agent for migraine prevention were published. In the same year, a randomized, double-blind, placebo-controlled study was carried out, which confirmed the efficacy of botulinum in preventing migraine. Since then, several clinical trials and meta-analyses have shown that botulinum toxin injections effectively reduce the frequency, severity, and duration of headaches in patients with chronic migraine (AISHA et al, 2023).

Botulinum toxin (TB) is produced by the gram-positive and anaerobic bacterium Clostridium botulinum, belonging to the Clostridiaceae family, developed in an amine medium and yeast extract. Currently, eight immunologically distinct serotypes of botulinum toxin have been identified, of these, seven serotypes (A, B, C1, D, E, F and G) are classified as neurotoxins that differ serologically due to their phenotypic and genetic characteristics. Type A and B neurotoxins have been widely used both in aesthetics and in therapeutic procedures. However, only type A neurotoxin, commercially presented as BOTOX® or OnabotulinumtoxinA, is used in migraine prophylaxis (ARAUJO et al, 2017).

Toxin type A (TBA) is divided into five subtypes (A1, A2, A3, A4, A5) that differentiate according to amino acid sequences, and these differences may determine the immunological and biological properties of the toxin. Among the five subtypes, only A1, A2 and A5 are purified forms that have been analyzed at an amino acid sequencing level (METELO et al, 2014). The purification

of the toxin is extremely important to avoid any type of adverse reactions and prevent the increase in antigenicity, and for this it is essential to leave the toxin free of ribonucleic acids and contaminating materials by removing these residues. This process occurs through precipitation of the culture solution in an acid medium, until the acquisition of a crystalline compound formed by a high molecular weight protein associated with hemagglutin. The acquired compound is redissolved in saline solution integrating albumin and then sterile filtered before vacuum freezing (ARAUJO et al, 2017).

The neurotoxins produced by C. botulinum are synthesized in the form of a 150 kDa polypeptide chain, composed of a 50 kDa light chain and a 100 kDa heavy chain joined by a non-covalent disulfide bond, associated with a zinc atom. The heavy chain can be functionally divided into two domains, an amine terminal domain, with cellular and homologous function in the various types of toxin, and a carboxyl terminal domain, associated with membrane fusion activity and ion channel formation. The toxicity of TB is due to the activity of a zinc-dependent metalloprotease, located in the light chain. This chain has a proteolytic activity that cleaves the target neuronal proteins, that is, it cleaves the SNARE (soluble N-ethylmaleimide-sensitive fusion attachment protein receptor) complex, made up of complex proteins that are critical for the release of the neurotransmitter acetylcholine (ACh). After its synthesis, this molecular part is associated with non-toxic proteins, which have, among other properties, hemagglutinin. These proteins associate in order to stabilize and protect molecules from temperature changes, pH decreases, and enzymatic degradation (METELO et al, 2014).

One mechanism of the analgesic effect of TBA is believed to be the inhibition of the release of certain pain neurotransmitters, such as Substance P, calcitonin gene-related peptide (CGRP), and glutamate, which are involved in the transmission of pain signals during a migraine attack. A second mechanism proposed for the analgesic effect of TB is to control the expression of pain receptors on the surface of neurons. For example, some studies have discussed the role of toxin A in the treatment of migraine through a mechanism of modulating ion channel expression in nociceptors. Although the effects of botulinum toxin A on ion channel expression in nociceptors have not been directly investigated in people with migraine, studies in patients with overactive bladder suggest that it may

reduce and normalize levels of vanilloid 1 (TRPV1) and purinergic (P2X3) receptors. Botulinum toxin may also have a third antinociceptive mechanism related to its effect on the central nervous system. This was demonstrated in rat studies, where the toxin affected pain on the opposite side of the body to the injection site. The toxin is believed to be transported from the injection site to the central nervous system, but the mechanism of this action has yet to be clarified (AISHA et al, 2023).

Some clinical studies show that BTA is effective soon after the first application. The duration of its effects can be observed from four to six months after treatment, depending on the dose, metabolism of each patient, severity of the clinical condition, capacity for neurological regeneration and whether or not other therapies are used. The applications are usually made in the frontal area, nape and temporalis muscle, are administered intramuscularly, with fixed doses between 155U and 195U, performed bilaterally, divided from the head and neck on the right and left side. There must be defined care, the diagnosis must be made by a specialist and the BTA must always be administered with maximum supervision. In case of overdose due to application in the wrong muscle or by injection, there is the possibility of administering botulinum antitoxin within 21 hours after application, in order to block or reduce the effect of TBA (ARAUJO et al, 2017).

Usually, botulinum toxin is well tolerated, and adverse outcomes are rare and short-lived, directed at muscle weakness and pain at the injection site. The effect decreases with increasing distance from the injection site, however, when injected in large volume, it can be dispersed to nearby muscles. Eventually, momentary bruising may occur at the injection site or the injection is followed by rapid pain or headache [6]. Other, less common, side effects include transient increase in intraocular pressure and secondary biliary colic. Most events are associated with the region in which the injection is administered, being one of the crucial points for the occurrence of the reduction of adverse effects (METELO et al, 2014).

RESULTS AND DISCUSSIONS

Current migraine preventive therapies are often unsatisfactory due to their limited efficacy, adverse effects, and drug interactions. To evaluate the efficacy of botulinum toxin A in the prophylactic treatment of migraine, Silberstein et al. (2001) conducted a double-blind, randomized study with 123 patients who had a history of two to eight moderate to severe migraine attacks per month, with or without aura. During the study, participants were randomized to receive single administrations of placebo or botulinum toxin type A, at a dosage of 25 U and 75 U, injected at various sites of the pericranial muscles. Over the course of 3 months after the injections, participants recorded the frequency, severity, and occurrence of symptoms associated with migraine. Compared to the placebo group, subjects in the 25-U TBA treatment group showed significantly fewer migraine attacks per month, a reduced severity, a reduced number of days using acute medications, and a reduced incidence of migraine-associated vomiting. Regardless of the dose, both groups that received the toxin treatment achieved significant improvement when compared to the placebo group. In addition, treatment with TBA was well tolerated, only the group that received the 75 U dosage exhibited a higher rate of treatment-related adverse events compared to the placebo group (SILBERSTEIN et al, 2001)

Similarly, a study conducted by Anand et al. (2006) suggested some benefits in the use of BTA in migraine patients. The randomized, double-blind, vehicle-controlled study was conducted in 32 patients with a history of 2 to 8 episodes of migraine attacks per month, with or without aura. Participants were randomized to receive single administrations of 50-U or placebo injected at multiple sites of the pericranial muscles. Patients kept diaries in which they recorded outcome measures such as frequency, severity, and occurrence of symptoms associated with migraine. About 75% of patients reported complete headache relief after administration of TBA and no improvement was observed by the placebo group. Quality of life parameters were also evaluated, and showed a considerable improvement. No adverse effects were reported in either group during the study. It is evident from the study that pericranial injection of 50-U of TBA showed good efficacy and tolerability as a prophylactic

agent in migraine (ANAND et al, 2006)

In this same perspective, a study conducted by Robertson and Garza (2012) also reported the effectiveness of the use of BTA. For four months, 41 migraine patients participated in the research in order to understand the effectiveness of TB for the treatment of chronic migraine. These patients were randomly assigned to either 100U of onabotulinumtoxinA or placebo. The doses were fixed and applied to the glabella, temporalis, frontal, suboccipital and trapezius muscles. Patients who used caffeine and analgesics were excluded. According to the research, headaches decreased significantly after the injection of TB-A, with the frequency of reduction of episodes from 13.8 to 10.1 episodes per month. Comparatively, patients who had been treated with placebo had an increase in migraine frequency from 14.6 episodes to 15.4 per month (ROBERTSON et al, 2012)

Similar results were demonstrated in a prospective study by Burstein, Dodick, and Silberstein. In order not to influence the results intended in this study, patients who only had tension headache, peripheral nervous system lesions or who had taken opioids were not included. The total number of patients in this study was then 82 individuals with migraine, mostly women, whose ages ranged from 21 to 75 years. Participants had a history of migraine attacks, starting at 19 and 21 years of age, 33% had an episodic migraine (about 8 episodes per month) and 67% had chronic migraine (about 26 episodes per month). After administration of TBA, the average number of days of migraine episodes per month decreased by about 43%. Greater results were observed in patients who classified their pain as explosive. These results suggest that the efficacy of TB-A in migraine therapy may also be associated with the type of pain presented by the patient (BURSTEIN et al, 2010).

Although randomized placebo studies have shown its clinical efficacy, the mechanisms by which it exerts its therapeutic effect are still poorly understood and debated. In this regard, a study conducted by Sebastianelli et al. (2023) evaluated the cephalic and extracephalic nociceptive and lemniscal sensory systems in 15 patients with chronic migraine, using electrophysiological techniques before and after 3 months after a session of pericranial injections of OnabotulinumtoxinA (BoNT-A). The nociceptive blink reflex (nBR), the trigeminal-cervical reflex (nTCR), the pain-related cortical

evoked potential (PREP), and the somatosensory evoked potential of the upper limb (SSEP) were recorded. Three months after a single session of prophylactic therapy with BoNT-A in migraine patients, an increase in homolateral and contralateral nBR AUC, an increase in contralateral nBR AUC habituation slope and nTCR habituation slope, a decrease in 1st and 2nd block of PREP NP amplitude, and no effect on SSEP were found. These results provide electrophysiological evidence for the ability of a single session of BoNT-A injections to exert a neuromodulatory effect at the level of the trigeminal system through a reduction in the entry of meningeal and other trigeminovascular nociceptors. In addition, by reducing activity in the cortical areas of pain processing, BoNT-A restores normal functioning of descending pain modulation systems (SEBASTIANELLI et al, 2023).

FINAL CONSIDERATIONS

Current migraine preventive therapies are often unsatisfactory due to their limited efficacy, adverse effects, and drug interactions. It was observed that patients treated with botulinum toxin type A had significantly fewer migraine attacks per month, a reduced severity, a reduced number of days using acute medications, and a reduced incidence of migraine-associated vomiting. In addition, the results demonstrated good efficacy and tolerability in the use of BTA as a prophylactic agent in migraine. Although the use of onabotulinum toxin has shown benefits in migraine patients, it has a higher cost and, therefore, its access is restricted to a few patients, since it is not available in the SUS or in the list of minimum coverage of health plans (NACAZUME, 2019).

REFERENCES

NACAZUME, J. Treatment and prophylaxis of migraine in Brazil: current scenario and new perspectives. Final Paper of the Pharmacy-Biochemistry Course of the Faculty of Pharmaceutical Sciences of the University of São Paulo. São Paulo, 2019.

OLIVEIRA, A. B.; QUEIROZ, L. P.; PERES, M. F. P. Annual Indirect Costs Secondary to Headache Disability in Brazil. In IHC 2019 Abstracts. Cephalalgia, v. 39, n. 1_suppl, p. 1–337, 1 set. 2019.

PIOVESAN, E.; CADECARO, P.; PEPE, C. Cost-effectiveness analysis of onabotulinum toxin A in the preventive treatment of chronic migraine from the perspective of the private health system in Brazil. Brazilian Journal of Health Economics, v. 9, n. Suppl1, p. 71–80, 2017.

YUAN, H.; SILBERSTEIN, S. The Use of Botulinum Toxin in the Management of Headache Disorders. Springer, 2020.

AISHA, Z.; ALTYNAY, K.; BAZBEK, D. Beyond aesthetics: expanding the applications of botulinum neurotoxins in chronic migraine medicine. European Journal of Neuroscience, 2023.

ARAÚJO, L. The use of botulinum toxin in the treatment of migraine. Bachelor's Degree in Biomedicine. Brasilia, 2017.

METELO, C. Therapeutic Applications of Botulinum Toxin, 2014. Integrated Master's Dissertation in Pharmaceutical Sciences at the Instituto Superior de Ciências da Saúde Egas Moniz, Portugal, 2014.

SILBERSTEIN, S. et al. Botulinum Toxin Type A as a Migraine Preventive Treatment. The Journal of Head and Face Pain, 2001.

ANAND, K. et al. Botulinum Toxin Type A in Prophylactic Treatment of Migraine. American Journal of Therapeutics, 2006.

ROBERTSON, E.; GARZA, I. Critical analysis of the use of onabotulinumtoxinA (botulinum toxin type A) in migraine. Neuropsychiatric Disease and Treatment, 2012.

BURSTEIN, R.; DODICK, D.; SILBERSTEIN, S. Migrain prophylaxis with Botulinum Toxin A is associated witch perception of headache. NIH, 2010.

SEBASTIANELLI, G. et al. Effects of Botulinum Toxin Type A on the Nociceptive and Lemniscal Somatosensory Systems in Chronic Migraine: An Electrophysiological Study. Toxins, 2023.