Editorial

Botulinum toxin A for the treatment of first bite syndrome

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We read with colossal interest the manuscript of Shaikh *et al.* entitled "*Botulinum toxin A for the treatment of first bite syndrome—a systematic review*" (1). The authors' systematic review results suggest that botulinum toxin (BT) A can be a potentially safe, effective treatment for the First bite Syndrome (FBS). The MEDLINE, Embase, Cochrane Base (CENTRAL), and Google Scholar were searched from inception until July 2020. Search results yielded 41 studies. There were no reported injection complications, including facial paralysis, infection, injection site reaction, and allergic reaction.

BT is gram-positive anaerobic Clostridium botulinum bacilli exotoxin. Several serotypes of the BT are known: A, B, C1, C2, D, E, F, and G. Botulinum toxin type A (BTA) is commonly used in medicine due to the long duration of the effects (2,3). In 1953, Brooks showed that injection of BTA into muscle tissue blocks the release of acetylcholine in the neuromuscular plaque and causes motor nerve fiber to become immobilized (2). In addition, BTA inhibits synaptosomal nerve-related protein 25 (SNAP-25), botulinum toxin type B (BTB) inhibits synaptobrevin, and botulinum toxin type C (BTC) inhibits syntaxin. These proteins are involved in the release of acetylcholine-filled vesicles into the synaptic cleft. Therefore, each BT serotype acts on different proteins involved in this process. Still, the effect of each is the same, i.e., blocking the release of the neurotransmitter into the synaptic cleft (2,4).

BT has a wide range of both cosmetic and therapeutic effects. Clinically, BTA and BTB are used. In recent years, its effectiveness has been proven in treating many diseases (4,5). Particular interest has been observed in the treatment of pain syndromes. It is a group of disorders where the pain is the primary symptom. In this case, the pain is chronic and neuropathic, i.e., caused by a pathological change or a disease in the somatosensory system. Most often, such pain is described by patients as burning, burning. Additionally, allodynia, hyperalgesia, hyperesthesia, or dysaesthesia often coexist (6).

The pathology may concern the peripheral system (peripheral nerves, nerve roots, nerve plexuses) and the central nervous system (spinal cord, brainstem, thalamus). In the case of peripheral neuralgia, damage to the peripheral nervous system leads to irritation of nerve endings and the accumulation of nociceptive compounds, i.e., substance P, bradykinin, glutamate, and peptide related to the calcitonin gene (CGRP). Accumulating pain modulators and focal inflammation lower the pain threshold of peripheral nerves per pain stimulus. Then it comes to the so-called peripheral sensitization. Peripheral sensitization also increases the influx of nociceptive compounds into the spinal cord, which leads to secondary sensitization of the spinal cord, i.e., central sensitization. Continuous peripheral and central sensitization leads to chronic pain. According to the efficacy criteria established by the American Academy of Neurology, botulinum toxin effectively treats post-herpetic, trigeminal, and post-traumatic neuralgia (level A of evidence of efficacy). In addition, BTA is also expected to be effective in the treatment of diabetic neuropathy, chronic lumbar spine

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pain, male pelvic pain syndrome, carpal tunnel syndrome, plantar fasciitis, knee replacement pain, post-traumatic neuropathic pain (evidence level B efficacy), and female pelvic pain syndrome, knee pain caused by osteoporosis (evidence of efficacy level C) (6).

Studies in cell cultures and animals show that BTA can affect pain transmitters in the peripheral and central nervous systems (6). In cell culture studies, the administration of botulinum toxin type A to neurons inhibits the release of calcitonin gene-related peptide (CGRP), glutamate, and other pain transmitters from nerve endings dorsal root ganglia of sensory fibers. BTA inhibits local, acute, and chronic inflammation within nerve endings by reducing the released transmitters, i.e., substance P or CGRP. In addition, in molar concentrations, BTA inhibits the functioning of membrane sodium channels in peripheral and sensory neurons. Properly functioning sodium channels are essential in pain signal transmission (6,7).

In recent years, there have been promising results of studies that indicate the possible effectiveness of BTA in the treatment of trigeminal neuralgia resistant to pharmacological therapy. Such a procedure would allow for safe treatment and reduced side effects associated with taking anti-epileptic drugs (8).

Contraindication to the use of botulinum toxin is myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis, use of anticoagulants, pregnancy or breastfeeding, severe airway obstruction, skin infection at the injection site (9).

Surgery in the head and neck area is associated with the risk of several complications, including cranial nerve dysfunction. FBS is one of those rare postoperative complications. FBS has been observed in patients after surgery on the parapharyngeal space and parotidectomy (10-16).

In the case of FBS, patients complain of acute pain in the preauricular or mandibular region, which appears at the first bite of food and decreases throughout a meal. Moreover, it can significantly worsen the patients' quality of life and sometimes reduce the need for continual dietary modifications. It is worth noting that there are cases of patients in whom the event of FBS was not preceded by surgical treatment (12,17). According to the literature, the incidence of FBS is approximately 6–10% (17). The analysis of the data published so far does not define an effective method of treating FBS. The use of non-steroidal anti-inflammatory drugs, anesthetics, and dietary modification do not show the desired effect in treating FBS (18-21). According to the literature, better results of FBS treatment were obtained with anti-epileptic drugs and tricyclic antidepressants (18,20). Abdeldaoui *et al.* did not observe pain reduction in patients with FBS after attempts to excise the remnants of the parotid gland in patients after parotidectomy or tympanic plexus neurectomy (10). The results of studies and clinical observations published in recent years show the effectiveness of botulinum toxin type A in reducing pain in patients with FBS. Nevertheless, it requires further studies in large groups of patients (1).

Many people associate botulinum toxin primarily with an aesthetic application—that is, to reduce facial wrinkles. However, as our article proves, there is much information in the literature about the therapeutic use of botulinum toxin. The use of BTA in many diseases turns out to be a very effective and safe therapy. In addition, it reduces the incidence of side effects associated with invasive treatment or the administration of systemic drugs. Therefore, physicians need to be aware of the possibility of including botulinum toxin in the treatment regimen of selected diseases. Appropriate patient qualification for BTA treatment and the correct dose and injection technique allows for better control of selected diseases and brings great satisfaction to the patient and the physician.

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