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Clinical Aspects of the Use of Botulinum Toxin Type A in the Treatment of Dysfunction of the Masticatory System

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article

Abstract

The purpose of this work is to present a new, still experimental method of treating temporomandibular disorders (TMD) by injecting botulinum toxin Type A (TBX-A), using its effects not as a toxin but as a medication. The mechanism of TBX-A, indications and contraindications for its use, as well as possible side effects, are discussed. Temporomandibular disorders are of concern to approximately 70–80% of the population. The effect of botulinum toxin depends on blocking the release of acetylcholine from a presynaptic neuromuscular synapse and, in the autonomous system, blocking its release from post-ganglionic cholinergic neurons. In cases of long-term TMJ disorders, muscle activity increases and spastic contractions may even appear. TBX-A offers an opportunity for a normal social and family life for many patients suffering from masticatory system disorders (MSD), who have been isolated from the environment by pain. The study is based on a review of the literature and the authors' own experiences during several attempts to treat patients by this method. TBX-A is a safe medicine when the injection is performed by a well-trained physician (*Adv Clin Exp Med* 2016, 25, 3, 569–573).

Key words: botulinum toxin type A, dysfunction of the masticatory system, stomatognathic system.

The masticatory system (MS) is the morpho-functional complex of mutually interacting tissues and organs of the mouth and facial part of the skull, forming a functional unit controlled by the central nervous system involved in the act of chewing, initial digestion, swallowing, the formation of sounds, breathing and participating in the expression of emotions. The individual components of this system interact with each other, creating a biological morphological-functional complex [1]. Dental articulation, the joints and chewing muscles are elements of the MS that are closely related both anatomically and topographically [2]. As a result of parafunctional activity, excessive and prolonged muscle tension can occur around the temporomandibular joint (TMJ), the suboccipital muscles, the cervical spine and, frequently, the shoulder girdle muscles. In addition, an overload of the TMJ is observed. The oral cavity of patients with an overloaded TMJ usually shows character-

istic wear of the incisal and occlusal surfaces of the teeth, cervical lesions as well as periodontal damage and atrophy [3]. These pathological changes can be very extensive. The systemic and external symptoms of masticatory system disorders (MSD) also include headache, neck and back pain, earache, tinnitus and hearing disorders, hypertrophy of the masseter and temporal muscles (a so-called “square-shaped face”), soreness in the region of the attachment points of the masseter and temporal muscles and an increase in tension and pain in the muscles of the shoulder girdle.

The symptom of temporomandibular disorder (TMD) that usually make patients seek medical help is pain, which can take the form of severe headaches, often confused with migraine headaches, and/or facial pain. In general, TMD patients are adults, but TMD can occur also in childhood [8, 10]. It is generally the result of the coexistence of at least few of the factors that pre-

dispose an individual to the development of this disorder. The most common are occlusal factors, tissue susceptibility, posture defects and stress, which causes long-term tension as a result of an inability to adapt to the rapid cultural and social changes. The problems of TMD affect approximately 70–80% of the population. Therefore, TMD is a global public health problem [1, 3, 6].

Botulinum toxin (TBX) is a strong biological exotoxin produced by *Clostridium botulinum*, a Gram-positive anaerobic bacterium. There are seven types of botulinum toxin, specified by the letters A to G, among which the strongest organic toxin is TBX-A. It can cause symptoms of poisoning – so-called “botulism” [3]. Botulinum toxin was discovered in 1817 by a German doctor, Justin Kerner, while examining a patient who had died as a result of poisoning from a moldy sausage [2]. The possibility of using botulinum toxin in medicine was demonstrated for the first time in 1981 by Alan Scott. Using local injections of botulinum toxin he selectively inactivated muscle spasticity in strabismus [2, 8].

Currently, TBX-A is becoming a widely used substance in general and esthetic medicine. The purpose of this article is to present a new, still experimental method of treatment of TMD by injecting TBX-A.

The effect of botulinum toxin is related to blocking the release of acetylcholine from a pre-synaptic neuromuscular synapse and, in the autonomous system, blocking its release from post-ganglionic cholinergic neurons. With respect to MSDs, TBX-A is used to treat bruxism, myofascial pain, disorders associated with TMJ disc displacement and habitual dislocation of the mandible. The neurotoxin produces dose-related weakness or paralysis of skeletal muscles by blocking calcium-dependent acetylcholine from nerve endings, causing “functional denervation”. The local paralysis is reversible; neuron regrowth occurs after 2–4 months. Muscles treated with TBX-A are less sensitive to palpation [4]. Its effect provides the possibility of inactivating a hyperactive muscle without affecting muscles not subject to spasticity or those in which it is desirable. Not only is its effect reversible; it also has a high safety factor and a negligible number of side effects [5]. In the treatment of spasticity it provides a so-called “therapeutic window” for physiotherapy during the months following treatment. At the proper doses, TBX-A reduces muscle tension without weakening the muscle, which creates a good situation for restoring its function. It causes no permanent effect within the muscle, and a few years after the injection, the neuromuscular organ returns to normal. In addition,

it does not cause pain, necrosis or inflammation of the muscle [5].

Diagnoses of masticatory system disorders are based on clinical examination of the patient [2, 6, 7], the occurrence of characteristic asymmetric values of the Bennet angle, and on the basis of additional tests, such as EMG, kinetography, MRI, axiography, T-scan occlusal analysis and sonography. Because of its neurotoxic effects, the use of TBX-A during the treatment of MSDs requires very thorough medical records, which include information on the condition of the muscles before treatment, determination of the purpose of treatment, the name of the TBX-A medicine used, the dose, the dilution and the names of the muscles it is injected into – the amount of the drug per muscle and the number of points of injection.

Contraindications to the Use of Botulinum Toxin

Treatment with botulinum toxin is contraindicated in women during pregnancy and lactation, in patients with known hypersensitivity to any component of the drug (especially hypersensitivity to human albumin), during an infection or inflammation of the area where the toxin injections are planned, in patients with musculoskeletal conduction disorders, in primary muscular disorders (muscular dystrophy, neuromyopathy, congenital myopathies, myotonic disorders, mitochondrial myopathy and unspecified or other primary muscle disorders). It is also contraindicated in patients being treated with aminoglycoside antibiotics, ciclosporin, D-penicillamine, tubocurarine, pancuronium, galamine, succinylcholine, chloroquine or hydroxychloroquine [2]. Because of the hemagglutinin content, the risk of transmission of a viral infection cannot be eliminated with certainty. Before application of the medicine, the availability of anti-allergic drugs should be ensured.

Immunogenicity

Botulinum toxin has immunogenic properties, which may lead to the stimulation of antibody production. Antibodies can be either neutralizing (which interfere with the activity of the drug and reduce the effectiveness of the treatment) or non-neutralizing (which do not affect the drug), and are formed in response to repeated exposure to the neurotoxin protein complex. The appearance of antibodies against one of serotypes of botulinum

toxin does not preclude an effective response to the other serotypes. To minimize resistance to the botulinum toxin resulting from the production of autoantibodies, the lowest effective dose should be applied, with at least three-month breaks. Booster injections are not recommended [8].

To treat MSDs, the injections are performed with a 12mm needle, with a force of 30 g, strictly intramuscularly, after careful aspiration, bearing in mind that the width and thickness of the muscle vary individually. The muscle must be relaxed [1]. While the neurotoxin is being injected, the patient should sit in the dental chair and after the injection must remain in an upright position for up to four hours in order to reduce diffusion to the throat muscles, which can involve the risk of reflux [9]. Usually, the medicine is injected into the masseter or temporal muscles (in the treatment of bruxism), and in rare cases, the lateral pterygoid muscle [10].

TBX-A injection is particularly effective for patients in whom occlusal splints cannot be applied or their effectiveness is insufficient. Sometimes TBX-A injection into the masseter muscle above the angle of the mandible is sufficient (in patients not reacting after injury to the CNS) [10]. Myofascial pain, characteristic of MSD, is related to the presence of trigger points in muscle bundles. These are sensitive areas in muscles of increased tonus, causing radiating pain while pressing them [11].

Analgesics initially provide pain relief to the trigger points. Pain in the TMJ is decreased after steroid injection, causing stretching and hydrodissection inside the structure [12]. Three trigger points are located in the superficial layer of the masticator muscle, with the pain referred to:

- 1) the mandible, temporal and frontal bones;
- 2) the mandibular molars; and
- 3) the maxillary molars and infraorbital area.

The trigger point in the deep layer of the masseter muscle affects the ear and the TMJ area. TBX-A is applied intramuscularly. The masseter muscle is divided into five points, and the drug is injected into the largest cross-section [6]. The total dose of TBX-A for the masseter muscle is 50 TBX-A units/1 mL of physiological saline (NaCl solution). The injection is done with EMG monitoring. Patients with unilateral or bilateral muscle disorders should always have the drug injected on both sides [9].

The temporal muscle may have four active trigger points, from which the pain radiates to:

- 1) the maxillary incisors;
- 2) the muscles;
- 3) the maxillary premolars and infraorbital area; and
- 4) the maxillary molars and TMJ area.

The total dose of TBX-A for the temporal muscle is 50 units/1 mL of NaCl solution [3].

The medial pterygoid muscle trigger points refer pain to the ear, the TMJ, the hard palate and the dorsal area of throat. Less often, because of the technical difficulties, the lateral pterygoid muscle is subjected to a blockade. It can be found by palpation in the direction of the lateral lamina of the pterygoideus. The needle is inserted between this structure and the coronoid process of the jaw parallel to the length of the muscle [13].

In patients diagnosed with an MSD, the TBX-A injection should be applied to the superior lateral pterygoid muscle, which stabilizes the head of the mandible and the articular disc. This muscle connects to the TMJ disc and the condylar neck. The therapeutic effect of the treatment lasts for 3–6 months and may be permanent, if the ligaments in the TMJ undergo complete fibrosis. In cases of bruxism unaffected by classical methods of treatment, the TBX-A injection should be applied to the masseter and temporal muscles. TBX-A therapy brings a double benefit: In addition to relieving pain, it improves esthetics by reducing the cross section of the masseter muscle [8].

TBX-A is used in the treatment of disorders associated with TMJ disk displacement and in the treatment of habitual dislocation of the mandible following dysfunction of the lateral pterygoid muscles [12, 13]. To treat dislocation of the disc Bakke et al. applied 30 units of TBX-A to the lateral pterygoid muscle twice, at 6-month intervals, under EMG monitoring. During a one-year follow-up period there was no recurrence of symptoms [7].

Habitual dislocation of the mandible is an indication for an extraoral injection in the space formed by the zygomatic arch and the mandibular notch. Reports in the literature state that two injections are normally performed to a depth of 3–4 cm, 1 cm below the central part of the zygomatic arch and 0.5–1 cm outward from that point, just in front of the condylar processes of the mandible. Before the injection, the mandible is placed back in its position, and after the botulinum toxin application, it is immobilized with an elastic band for 4–5 days [4, 11]. For TMJ disc dislocation it is sufficient to use a TBX-A injection in the lateral pterygoid muscle. The effect is maintained for 2–4 months [10].

The effectiveness of TBX-A is demonstrated by reports of studies carried out by clinicians [1, 2, 13]. In double-blind trials the experiments are always randomized, and patients are not aware of what drug (TBX or placebo) they have been injected with. TBX-A and saline (NaCl) have similar physical characteristics; both solutions are colorless and odorless.

TBX-A is used in patients with chronic hyperactivity of muscles of mastication. According to research by von Lindern et al., TBX-A reduced pain in 91% of the patients in a study group of 90 people with chronic facial pain accompanying over tensed muscles of mastication [8]. In the placebo group von Lindern et al. noted relief in less than 0.01% of the patients; in the study group, relief was observed in 19 cases after two months, while in the rest of participants, relief was noted after one to three months of treatment with TBX-A. To evaluate the effectiveness of therapy with TBX-A, Ernberg et al. used the VAS (Visual Analogue Scale), which expresses the subjective feeling of pain experienced by the patient. Patients diagnosed with MSDs were assessed twice a day, in the morning and in the evening, ranking the pain intensity on a scale of 0–10, where 0 is no pain and 10 is the worst imaginable pain [4]. In this way, a pain relief scale (PRS) was developed, which specifies the impact of pain on daily activities and the number of days on which patients refrained from their usual activities (work, school, household chores, etc.). The assessment covered all the points of injection. Check-ups were performed at intervals of two weeks; the total duration of the study was 8 weeks. TBX-A induced muscle relaxation an average of one week after injection, which resulted in muscle pain relief.

In studies by Pihut et al., the efficiency of TBX-A injection was confirmed by decreased scores on the VAS, functional testing, electromyography tests, correct potentials of masseter muscles and symmetrical contractions of the right and left masseter muscle [3, 6].

The therapeutic effect of TBX-A depends on the dose, injection technique and the size of the muscle [5]. The effect of the injection is usually temporary. Injections should be repeated, although there are a few reports of permanent results through the elimination of pathological muscle memory and restoration of physiological pattern [2, 4]. These observations and results suggest a positive therapeutic effect of repeated injections of TBX-A on MSDs.

According to some authors, the diagnosis “bruxism” is overused (5, 8). In their view, bruxism refers only to a few percent of the population,

and not, as claimed by others, to 65–80%. In consideration of these differences, it is difficult to formulate an opinion on the effectiveness of treating bruxism by TBX-A injection [2].

In TMJ disc dislocation, TBX-A injection is regarded as one of the conservative treatments of this condition. According to other authors [3, 6, 12] a recommended treatment is Dautrey’s procedure, which consists of joining the displaced zygomatic arch and the lateral part of the joint with a mini-plate. Injection of TBX-A, like the use of analgesics, is just an additional method of treating the closed lock. A retrospective cohort study involving patients with head and neck cancer confirmed the advantages of MSD therapy combining “dyno-splints”, analgesics and TBX-A, but according to Stubblefield et al. the effects of TBX-A are difficult to interpret, because the simple application of a puncture – the injection itself – leads to a reduction in muscle tension and bruxism [11].

TBX-A can be a powerful allergen, and research on its use is still ongoing. The literature also mentions other side effects following the injection of TBX-A: fatigue, headache, muscle weakness, flu-like symptoms, dry mouth, and pruritus [2, 4, 6, 13]. Incorrect deposition of TBX-A to the vascular system causes the symptoms of botulism. Extraoral injections are difficult and carry the risk of hemorrhage, eg. when the maxillary artery or venous plexus is damaged. According to Ernberg et al., the results of treating patients with myofascial pain with TBX-A are encouraging, but they are not devoid of systemic side effects in the form of temporary weakness or nausea [4]. The side effects of injection in the case of one patient included difficulty in swallowing, paralysis of the TMD muscles and facial changes; these symptoms resolved after four weeks [4].

In cases of long-term TMJ disorders, increased muscle activity and even spastic contractions may occur as an effect of malocclusion. TBX-A offers an opportunity for a normal social and family life for many patients who have been isolated from the environment by pain. TBX-A is a safe drug when the injection is performed by a well-trained physician. Principles of training are being developed by a group of experts and include the completion of both theoretical and practical courses.

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