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Use of a botulinum toxin A in dentistry and oral and maxillofacial surgery

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Botulinum toxin (BT) was the first toxin to be used in the history of human medicine. Among the eight known serotypes of this toxin, those currently used in medicine are types A and B. This review article mainly discusses BT type A (BTA) because it is usually used in dentistry including dental anesthesiology and oral and maxillofacial surgery. BTA has been used mainly in the treatment of temporomandibular joint disorder (TMD) and hypertrophy and hyperactivity of the masticatory muscles, along with being a therapeutic option to relieve pain and help in functional recovery from dental and oral and maxillofacial surgery. However, it is currently used broadly for cosmetic purposes such as reducing facial wrinkles and asymmetry. Although the therapeutic effect of BTA is temporary and relatively safe, it is essential to have knowledge about related anatomy, as well as the systemic and local adverse effects of medications that are applied to the face.

Keywords: Botulinum toxin; Botulinum toxin, type A; Dentistry; Oral and Maxillofacial Surgeons.

History of medical use of botulinum toxin (BT)

Botulism is derived from the Latin word botulus, which means black sausage, and has been known as food poisoning caused by the ingestion of rotten meat. Botulinum toxin (BT), initially found in rotten sausage, induces food poisoning, which leads to mydriasis and skeletal muscle paralysis. This toxin was initially reported by Justinus Kerner in 1817, and the possibility of using it to relax the hyperactivated motor system was subsequently reported [1,2]. Van Ermengem, a Belgian microbiologist, succeeded in isolating a pathogen from the feces of a patient who ingested rotten sausage in 1897, and named it Bacillus botulinus, which was renamed Clostridium botulinum in 1922. Further, the study was translated and published in English in 1979 [3]. Schantz succeeded in producing massive amounts of BT, and the discovery by Burgen that BT played a role in presynaptic acetylcholine inhibition in 1949 laid the foundation for the clinical application of this toxin [4]. BT type A (BTA) was initially used by Scott [5-7] in 1973 and became the first toxin to be adopted in medicine, with the approval by the US Food and Drug Administration (FDA) in the treatment of adult strabismus and blepharospasm in 1989. Subsequently, while treating a patient with blepharospasm using BTA, Carruthers and Carruthers [8] serendipitously discovered that it reduced the appearance of wrinkles in the glabellar region. They reported that this resulted from the relaxation of the muscles that control facial expressions. Then, they found that it was also effective on wrinkles around the eyes and the nasolabial

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folds [8]. Since then, the scope of BT application has expanded to treatment of ophthalmological disorders such as blepharospasm and neurological disorders such as facial spasms and cervical and limb dystonia, and it has been mainly used to relieve inappropriate or excessive tension in the skeletal muscles. Additionally, it has been reported to be effective on the smooth muscles of the gastrointestinal tract [7,9-11]. Furthermore, its range of application was recently expanded to the treatment of pain caused by increased tension of the masticatory muscles, facial asymmetry, hyperhidrosis, and osmidrosis, as well as the cosmetic reduction of masticatory and calf muscles [10,12].

Structure and types of toxin

BT is a neurotoxin secreted by the anaerobic bacterium *Clostridium botulinum*, having eight serologic types (A, B, C1, C2, D, E, F, and G). The molecular weight is approximately 150 kDa, consisting of 100 and 50 kDa heavy and light chains, respectively. The eight serotypes of BT have similar molecular structures and functions. The serotypes that are harmful to the human neurological system are A, B, E, F, and G, and BTA has the strongest toxicity. Although the spores of BTA and BTB are heat-tolerant, the neurotoxin is not. Furthermore, the toxin is intolerant to alkali but acid-resistant and, therefore, it is not degraded under acidic conditions [13,14]. BTA and BTB are clinically used [12], and their active regions are specific with a desirable effect that can be obtained by controlling the concentration. The most commonly used BTA products marketed worldwide are BOTOX® (Allergan, Inc., Irvine, CA, USA) and Dysport® (Ipsen Ltd., Maidenhead, Berkshire, UK), and for BTB, MYOBLOC® (Elan Pharmaceuticals, Inc., South San Francisco, CA, USA). MYOBLOC®, unlike BTA, is sold in the form of a solution and is mainly used in neurology. BOTOX® and Dysport® are in the form of a white power and are used after dilution. Because BOTOX® is 3–6 and 50–100 times more effective than comparable doses of Dysport® and MYOBLOC®, respectively, it is recommended to exercise caution when choosing the dose based on the product during treatment [15].

Mechanism of action

BT is known to cause muscular paralysis by its action on the neuromuscular junction (NMJ), where it blocks acetylcholine release in cholinergic neuron synapses. Following the injection of BT, its heavy chain attaches to presynaptic cholinergic motor nerve terminals in the NMJ, and subsequently enters the neuron by endocytosis. The light chain, which is released from the endosome into the cell cytoplasm, cleaves synaptosome-associated protein of 25 k Da (SNAP-25) involved in the exocytosis of acetylcholine. Consequently, BT causes muscular relaxation by blocking acetylcholine release from presynaptic nerve fibers in the NMJ and inhibiting the depolarization of postsynaptic nerve terminals [4,16,17]. BT does not inhibit the production of acetylcholine and, therefore, motor function is recovered by subsequent motor axon outgrowth step, which involves the sprouting of axons in the motor end plate after a certain time has elapsed after toxin injection [16].

Clinical application of BTA in dentistry and oral and maxillofacial surgery

Although BTA is currently the most commonly used toxin for the improvement of facial wrinkles, it has been conventionally used in the treatment of strabismus, bladder dystonia, and cervical dystonia. Furthermore, BTA is still used in the treatment of hyperhidrosis, voice cerebral palsy, and upper limb spasticity [18,19]. It is also used for both cosmetic and therapeutic purposes in dentistry including dental anesthesiology which for pain management and oral and maxillofacial surgery.

1. Cosmetic use of BTA

1.1. Facial wrinkles

The most common cosmetic indication of BTA is in wrinkle therapy for glabella lines and platysmal bands, and in perioral cosmetic therapies such as gummy and asymmetry smile treatment [20-22]. Wrinkles such as glabellar lines are a spontaneous facial animation that develops when the lower facial muscles pull the skin, and they develop mainly by the action of the procerus and corrugator supercilii muscles. In addition, this line becomes more obvious with aging and constant exercise [23]. BTA has been used to temporarily treat not only glabellar lines but also lateral cantonal lines called horizontal forehead lines, platysmal bands, perioral lines, and crow's feet. The efficacy of BTA in reducing facial wrinkles has been proven in randomized controlled trials [24-26].

Administering BTA for wrinkle therapy is generally simple. An adequate dose is perpendicularly injected considering the anatomy of the region to be treated. BTA is known to diffuse to approximately 10 mm and, therefore, is injected at that distance from major structures such as the bony orbit [22].

Successful results have been reported in the treatment of not only glabellar lines but also vertical lip rhytids, mentalist wrinkling, lower eyelid orbiculares hypertrophy, and excessive gingival exposure (gummy smile), which can be treated by injecting the toxin into the lip to elevate the muscle [20,22-27].

1.2. Correction of prominent mandible angle and facial asymmetry due to masseter muscle hypertrophy

Although prominent mandible angle mainly develops skeletally, it can also develop by bilateral masseter muscle hypertrophy, and facial asymmetry develops with unilateral masseter muscle hypertrophy. In this case, a satisfactory therapeutic effect can be obtained using intramuscular BTA injections. In addition, injecting BTA into the masseter or temporalis muscle is effective in the treatment of bruxism [20,28-32].

2. Therapeutic use of BTA

Temporomandibular joint disorders (TMD), which are closely related to abnormalities in the masticatory muscles, are also treated by applying BTA [31,33]. Furthermore, successful results have been reported with this treatment strategy not only in basic experimental studies but also in the treatment of salivary gland secretory disorders such as sialorrhea and Frey syndrome with BTA [29,34]. Moreover, BTA is used in the treatment of facial pain and paralysis [35,36].

2.1. TMD

TMD is known to be closely associated with pain in the masticatory muscles adjacent to the temporomandibular joint (TMJ). BTA application in this condition has relieved the pain caused by hyperactivity in TMD as well as that in the masticatory muscles and has been successful in the treatment of TMJ dislocation [31,33,37-40]. Patients with TMD are usually administered BTA into the adjacent masticatory muscles such as the masseter and temporalis muscles. This strategy has successfully improved parafunction such as clenching as well as bruxism and TMD symptoms [33,37,41,42].

Patients with TMD often experience mouth-opening limitation, and BTA therapy can relax the adjacent masticatory muscles and, thereby, improve the muscle inflammation, leading to improved mouth opening. In addition, it has been reported that BTA injection into the masticatory muscles including the lateral pterygoid muscles has a favorable therapeutic effect [41,43,44].

2.2. Facial nerve palsy

Although most studies are case series, attempts have been made to treat facial paralysis with BTA. Inducing ptosis by temporarily paralyzing the muscle by injecting BTA in the levator palpebrae superoris can prevent drying of the cornea when the eyes cannot be closed normally because of facial nerve palsy [45,46]. A method for

treating patients with facial paralysis using BTA has been suggested, which induces facial symmetry by causing facial paralysis following the injection of BTA into the normal side of the patient's face [36,47-49].

2.3. An adjuvant for wound healing after oral and maxillofacial surgery

Inappropriate movements of the muscles adjacent to the surgical site immediately after surgery can inhibit healing. Pre- or post-operative BTA injections can facilitate healing by weakening these muscles. It has been reported that BTA injection into the masticatory muscles of patients with jaw fractures, which is the most common treatment in oral and maxillofacial surgery, prevents bone displacement. In addition, a successful result was obtained by injecting BTA into the masseter and temporalis muscles, which weakened the masticatory strength when immediate or delayed loading was performed after dental implantation [30,50].

3. Other applications

Successful results have been obtained by administering BTA in salivary gland secretory disorders such as sialorrhea and Frey syndrome, which are common in patients with Parkinson's disease. Post-traumatic sialoceles and cysts, which can develop in the damaged parotid gland duct during cancer resection surgery, can be also treated [29,34,51-55].

Higher doses of BTA are required for therapeutic purposes than those used for cosmetic purposes and, therefore, most complications develop with therapeutic use. Therefore, persons performing therapeutic procedure using BTA should exercise extreme caution and competency [20].

Complications

The complications of BTA injection can be classified into three, i.e., systemic, local, and reduced therapeutic effects due to antibody formation. Systemic complications develop mostly when an overdose of BTA is injected and include nausea, fatigue, malaise, flu-like symptoms such as fever and chills, increased blood pressure, diarrhea, abdominal pain, and anaphylaxis due to allergic reactions. Local complications, which can vary based on the injection site, include headache, pain at the injection site, edema, ecchymosis, ptosis, dry eye syndrome, lagophthalmos, orofacial edema, dysphonia, and sensory abnormality [2,56].

Headache is the most common adverse effect. Although BTA-induced headaches have been known to develop within 24 hours after the injection, they tend to reduce with increasing injection frequency. Therefore, it has been concluded that the headache is associated with the injection, based on an article reporting a meta-analysis [57]. Bruises or ecchymosis can develop in any area, and to prevent this, it is important to avoid superficial vessels by using the thinnest needle possible and bright light for adequate illumination during the procedure. Ptosis usually develops as the neurotoxin diffuses to adjacent areas when it is injected into the corrugator supercilii, and can be prevented by inhibiting toxin diffusion by pressing on the orbital rim with a finger [58]. BOTOX® is known to diffuse less than Dysport® does, and an ultra-concentrated technique, low injection volume, and shorter duration of effect are recommended to prevent diffusion. BTA is prohibited in patients with neuromuscular disorders such as peripheral motor neuropathies, Eaton-Lambert syndrome, multiple sclerosis, and myasthenia gravis [59].

Furthermore, BTA is a category C drug; therefore, it should not be prescribed for pregnant or nursing women. In addition, extreme caution should be exercised in patients with systemic diseases such as asthma and arrhythmia, who have been reported to exhibit high incidences of adverse effects [60]. According to the 2005 FDA report related to this, there were 1437 cases of adverse reactions to BTA injections from November 1989 to May 2005, and 28 of these patients have died. The causes of death were respiratory arrest (n = 6), myocardial infarction (n = 5), cerebrovascular accident (n = 3),

pulmonary embolism (n = 2), and others (n = 3). In addition, in all these cases BTA was used therapeutically and not for cosmetic purposes [60]. Furthermore, although drug interactions have not been reported clinically because very few diseases are clinically treated with BTA, the effect of the toxin can be enhanced in patients taking antibiotics (aminoglycosides and cyclosporine), muscle relaxants, calcium channel blockers, and other anticholinergic drugs while drugs belonging to the chloroquine class can decrease the effect of the toxin [59]. Similar to all foreign antigens, botulinum toxin also produces antibodies (neutralizing antibodies) that inhibit its therapeutic effect by inducing immune reactions in the body. Although 40-60% of patients have been reported to produce antibodies during BTA treatment, those that inhibit the therapeutic effects are produced only in 2-5% of patients [61,62]. The factors that increase the risks of producing neutralizing antibodies during BTA treatment include frequent BTA injection during a short period, high-dose injections, and increasing the dose of BTA injections [63]. In addition, a higher production of antibodies has been reported with BTB than with BTA [64]. Therefore, the dose used should be as low as possible in patients, and prolonging the period between injections can prevent antibody production. When the result of treatment is not effective, antibody production should be suspected, and when there is no reaction even after the dose is increased twice, and antibody test should be considered. If treatment fails because of antibody production, the product should be changed to another BT formulation.

Conclusion

Although there have been a number of preliminary studies on BT, most clinical studies have only reported the successful cases, and research studies showing a high level of scientific evidence have been very rare. To overcome this, a prospective, randomized, controlled study would be necessary.

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