Review

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The therapeutic use of botulinum toxin in different oral and maxillofacial conditions

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Abstract

Botulinum toxin A (BTx-A), a neurotoxin isolated from *Clostridium botulinum*, has been used for the treatment of a wide spectrum of conditions involving muscular spasm and hyperactivity, bruxism, in the management of temporomandibular joint disorders (TMD) related to muscle tension, fatigue, in cases of blepharospasm, strabismus, cervical dystonia, as a migraine preventive treatment etc. The established mechanism of the action of BTA is the inhibition of acetylcholine release from the motor nerve endings resulting in a locally decreased muscle contraction. Although the pathophysiology of myofascial pain remains uncertain, multiple neurologic, myogenous, and psychological theories have been accepted. Further evidence has suggested that the analgesic effects of Botox are mediated through the inhibition of the release of substance P and glutamate, which occurs at a lower concentration than the dose, necessary to produce muscle weakness. It could be used as a therapeutic option in functional recovery from dental, oral and maxillofacial surgery.

Myofascial pain disorders, in most cases, are due to muscle hyperactivity and could include malocclusion, TMJ internal derangement, cervical pain, psychological stressors and parafunctional habits. Patients non-responsive to conservative treatment modalities, even if etiological factors are eliminated, could be a therapeutic challenge to the clinician. The efficacy of trigger point intramuscular botulinum toxin injections in the management of myofascial pain is still controversial. A lot of clinical trials supported the efficacy of BTx-A in reducing the occlusal force and myofascial pain symptoms.

Keywords: botulinum toxin; bruxism; myofascial pain, temporomandibular joint disorders

Introduction

Botulinum toxin A (BTx-A) is currently used broadly for cosmetic purposes such as reducing facial wrinkles and asymmetry. Uses of BTx are continuously expanding. It has been used in the treatment of many diseases. Although the therapeutic effects of BTA are temporary and relatively safe, it is essential to have knowledge about systemic and local adverse effects of medications that are applied and proper indications

and contraindications of the procedure, as well as adequate anatomical knowledge.[1] While treating a patient with blepharospasm using BTx- A injection, Carruthers and Carruthers [2] determine that it causes a reduction the appearance of wrinkles in the glabellar region. They reported that this happened because of the relaxation of the muscles that cause facial expressions. They found that it was also effective on wrinkles around the eyes [2]. Since then, the range of BTx-A application has included treatment option for ophthalmological and neurological disorders such as strabismus, facial spasms and hemispasm, cervical and limb dystonia. It has been used to relieve inappropriate or excessive tension in the skeletal muscles. It has been reported the efficacy of BTx-A in the treatment of spastic smooth muscles of the gastrointestinal disorders [3]. In the last years, the range of application of botulinum toxin was expanded in the treatment of variety of medical disorders including pain syndromes, bruxism, facial asymmetry, hyperhidrosis, osmidrosis, muscle spasm, as well as the cosmetic reduction of masticatory and other muscles.[4, 5, 6, 7]

Aim

The aim of this review is to provide a better basis for indications, mechanism of action and clinical applications of botulinum toxin type A in the treatment of different medical conditions in the maxillofacial area and the beneficial effect of this drug on the state of muscle tension.

Results

BTx-A is a neurotoxin secreted by Clostridium botulinum, having eight serologic types -A, B, C1, C2, D, E, F, and G, which have similar molecular structures and functions. The serotypes that are harmful to the human neurological system(acetylcholine secretion) are A, B, E, F, and G, and BTx-A has the strongest toxic effect. The spores of BTA and BTB are heat-tolerant, but the neurotoxin is not. The toxin is intolerant to alkali but acid-resistant, and therefore it is not degraded under acidic conditions [5]

BT causes muscular relaxation by suppressing acetylcholine secretion from presynaptic nerve fibers in the neuromuscular junction and inhibiting the depolarization of postsynaptic nerve terminals, which leads to the induction of chemical denervation to paralyze muscle fibers [5, 7]. BTx does not inhibit the production of acetylcholine and, therefore, motor function is recovered over time. Skeletal muscle strength weakens 2-5 days after injection, minimize within two weeks and then gradually recovers. This effect continues from 6 weeks to 6 months as the injection dose influences the degree and period of denervation. Recovery is due to neuronal budding and regeneration of SNARE complexes. [5, 7, 8]. The method, dosage and frequency of BTx application could depend on the medical condition.

Clinical use of BTx-A in oral and maxillofacial surgery

Cosmetic use - correction of facial wrinkles, correction of prominent mandible angle and facial asymmetry due to masseter muscle hypertrophy, gingival smile etc.

Therapeutic use:

- TMJ disorders
- Facial nerve palsy
- Adjuvant treatment for wound healing after oral and maxillofacial surgery
- BTx- A injection into the masseter or temporalis muscle in the treatment of bruxism
- Salivary gland secretory disorders as sialorrhea and Frey syndrome, post-traumatic sialoceles and retention cysts [5]

Many treatment modalities have been advocated to arrest, stabilize, or reverse this muscle hyperactivity, ranging from conservative therapies such as heat, physical therapy, and splint therapy to more invasive measures such as oral medications, direct muscle injections, or dry needling. Although all of these treatment

modalities have shown some degree of success, all have potential complications. Splint therapy, for example, with an orthotic bite appliance, has been advocated for the treatment of bruxism and facial pain related to muscle hyperactivity. The bite appliance is thought to facilitate neuromuscular balance by eliminating occlusal interferences, resulting in a change in mechanical input to the periodontal proprioceptive fibers and thus the afferents in the jaw-closing muscles of mastication.[7, 8, 9] Although the effectiveness of oral appliances remains debatable, potentially serious side effects have been reported, including increased muscle activity, an increased load on the temporomandibular joint, and the supereruption of teeth. Furthermore, the variability in appliance design may contribute to the inconsistent success rate and complications. [10, 11, 12, 13, 14, 15].
Different modalities of treatment for the management of bruxism have been used as: occlusal splints, drugs(benzodiazepine or L-dopa), cognitive-behavioral therapy, but they have not been shown to be effective. The cause has not been eliminated, and the destructive effects of bruxism on anatomical structures prolong with time. Infiltrations with BTx-A in masseter and temporal muscle are a safe and effective procedure for patients with bruxism in clinical practice, especially in patients diagnosed with severe bruxism. [13,15]

The botox injection could be effective as treatment method in case of bruxism, than the classical conservative methods.The dose for masseter muscle is 25-30UI per side in 3 points and due to the stage of the condition we inject also the temporal musle with 15-20UI per side also in 4 main points.Two weeks after the application the patients complaints are subsided.The therapeutic effect is 8 up to 12 months without any affect of the chewing function.

Including criteria for patients with myofascial pain to be treated with BTx-A: failure to achieve satisfactory response to conservative therapies as: rest, habitual modifications, self exercises, office-based physical therapy program, medication (a non-steroidal anti-inflammatory drug with or without benzodiazepine), and either a 3-month period of occlusal splint therapy or a 3-month trial with Tricyclic antidepressants, constant pattern of pain localization and characteristics in at least two different clinical examinations, absence of concomitant intra-articular temporomandibular joint disorders. [5, 9, 18, 19, 20, 21, 22, 23] Patients with undefined pain patterns with poor localization are not good candidates for BTX injections.
All conservative therapies have to be discontinued when the decision to undergo BTA injections is made, which is usually several weeks before the injection appointment. An ampoule of 100 MU is diluted in 1 mL saline. The injections are made into points of tenderness in painful muscles and are individualized to each patient depending on the pain location and laterality. Only painful muscles are treated and as close as possible to the tender points. Patients should identify precisely the areas of pain by pointing with their fingers or hands; then, the surgeon has to palpate the tender spot and the surrounding areas, checking for additional tender points and possible referral points. The involved muscles have to be palpated during clenching and relaxation. BTx-A is injected directly into tender points in the affected muscles, with two to four injections for each muscle. In cases of myofascial pain with referral, no attempt has to be made to inject the distant sites the pain refers to. The most common areas the pain irradiates are the eyebrow, forehead, vertex, and occiput. All injections should be performed by one clinician and immediately after dilution of the toxin. Each injection point in affected muscles received 0.1 mL of a solution containing 10 UI of BTx-A. A 23G 30-mm-long needle could be used to inject the masseter, anterior portion of temporalis, sternocleidomastoid, and posterior digastric muscles and a 27G 15-mm- long needle- to inject the middle and posterior areas of the temporalis muscle. A 27G 37-mm audio-amplified electromyographic (EMG) needle should be used to inject the medial pterygoid muscle. The antero-inferior portion of the temporalis muscle could be injected at two different depths: a superficial injection at a depth of the medial surface of the zygomatic arch and a deep injection when the needle contacts bone at the outer surface of the lateral orbital wall.

All injections are performed transcutaneously. Patients are advised to close and open the mouth every 10 minutes in the next few hours following the injections, as muscular activity facilitates more efficient incorporation of toxin into the endplates and to use pain killers if required in the postinjection period. Muscle relaxants are not prescribed. [5, 8, 9, 18, 19, 23, 24]

Several studies have investigated the use of BTx-A for the treatment of myofascial pain, with positive findings. Acquadro and Borodic reported improved myofascial pain and tension headache symptoms after just 2 injections 4 weeks apart in the trapezius and splenius capitis. [1] Freund et al. [10] found a statistically significant improvement in pain, tenderness, function, and mouth opening in a cohort of 46 patients with an 8-week follow-up. Kamanly et al. suggest using of local anestetic or botulinum toxin injection for treatment of myofascial pain syndrome while BTx-A could be selectively used in patients resistant to conventional treatments.[16]

Similarly, Porta [17] compared the effects of Botox with those of a local anesthetic/steroid injection in a single-blinded study of 40 patients with myofascial pain and reported a statistically significant improvement after 60 days in the Botox group. Von Lindern et al. [19], in a single-blinded placebo-controlled study, reported a significant pain decrease after Botox injections in 90 patients with chronic facial pain.[19] In a double-blinded placebo-controlled randomized clinical trial, Kurtoglu et al. reported that, despite some return of muscle activity, there was a statistically significant longer-lasting improvement in pain and psychological status after Botox injections compared with placebo saline injections. [15]

Another study of 25 consecutive patients treated with botulinum revealed significant pain reduction in 69.2% of the patients with localized myofascial pain and 16.7% of the patients with referring myofascial pain (P = 0.015). Seventy-seven per cent of the patients with localized myofascial pain reported using less analgesic throughout the follow-up period, whereas only 25% of the patients with referring to myofascial pain. (P = 0.017). The effects of botulinum toxin in responsive patients subsided after a mean of 3.21 months. Patients with localized myofascial pain benefited from botulinum toxin injections, but patients with referring myofascial pain responded poorly to this treatment. [15]

Another medical condition that could be treated with BTx-A application is Frey's syndrome. It is a well-known sequel of operative procedures in the region of the parotid gland. It frequently occurs after conservative parotidectomies and occasionally after partial or radical excision of the parotid gland. The incidence depends on the size of the glandular compartment removed and on the accuracy of the diagnostic procedures used to verify the presence of the syndrome. Frey's syndrome occurs less frequently after purulent parotitis, tumours, trauma, typhoid fever, and irritation of the auriculo-temporal nerve by dislocated temporomandibular fractures. [25, 26]. Frey's syndrome becomes symptomatic when undesirable sweating occurs in the cheek and retroauricular and temporal regions after eating. Symptoms also can occur in the distribution of the greater auricular nerve. There can be flushing and warmness, with overheating of the affected areas of the skin, which in some cases is associated with pain. Pain also can occur as a preliminary sign or be the only symptom. Typically, the symptoms occur several weeks or months after surgery. Gustatory sweating can be verified by using the iodine-starch test, which shows the phenomenon on the basis of a colour reaction. Follow-up examinations show that approximately 30% to 50% of postparotidectomy patients experience the symptoms described, and approximately 15% rate their symptoms as severe. [27, 28]

In response to targeted questioning, 30% to 50% of postparotidectomy patients report having the typical symptoms. The minor iodine-starch test provides reliable verification of hyperhidrosis. In this test, the skin in the distribution of the auriculotemporal nerve is covered with a tincture of iodine and then with starch powder. One must be sure that the entire preauricular region up to the hair-covered temporal region and also the retroauricular skin are covered. After chewing a stimulant food, a bluish-black colour change ensures as sweat secretion increases.[26, 28]

The treatment of Frey's syndrome has been unsatisfactory. In addition to surgical measures such as excision of the affected skin or the interposition of fascia lata, muscle flaps (platysma), or Silastic sheeting (temporary), there is also medication involving the systemic or topical application of anticholinergics or antihidrotics. [25,26,27] The specific action of botulinum toxin on peripheral cholinergic synapses can be used while treating the disease. The primary effect is receptor-mediated endocytosis in the region of the synapses, followed by selective proteolysis of the vesicular synaptomal-associated protein (SNAP). This prevents the release of acetylcholine in the neuromuscular synaptic gap. The secretion of acetylcholine is similarly blocked at the cholinergic synapses of the autonomic nervous system [28, 29]. In this context, acetylcholine is the transmitter of the nerve innervation to the salivary and perspiratory glands. The fact that dry mouth is a primary symptom of botulism suggests the use of botulinum toxin for the treatment of Frey's syndrome. Early case studies referred to the use of botulinum toxin in the treatment of Frey's syndrome; later studies addressed treatment techniques and medium-term experience.[26, 27]
In facial palsy comlications as ipsilateral synkinesis or contralateral hyperkinesis botulinum toxin injection seems to be a minimally invasive technique which is helpful in restoring facial symmetry and balance of facial dynamic. [29,30] BTx-A application is useful in reducing muscular hyperkinesis and synkinesis in patients with residual facial asymmetry which may improve aesthetic and functional facial recovery.
Other complication in long-standing facial palsy is contracture of the muscles on the normal side causing difficulty in articulation, eating, drinking and esthetic concerns. By using BTx-A injection in overcontracted muscles(mainly smile muscles) could be restored symmetry to both active and passive movements.

The complications related to BTx-A injection can be classified into: systemic, local, and reduced therapeutic effects due to antibody formation. Systemic complications develop when an overdose of BTx-A is injected, and the symptoms include nausea, fatigue, malaise, flu-like symptoms, increased blood pressure, diarrhea, abdominal pain, and anaphylaxis. Local complications can vary depending on the injection site and could include headache, pain, edema, ecchymosis, ptosis, dry eye syndrome, lagophthalmos, orofacial edema, dysphonia, sensory abnormality, etc.[31]
BTx-A is prohibited in patients with neuromuscular disorders such as peripheral motor neuropathies, Eaton-Lambert syndrome, multiple sclerosis, and myasthenia gravis, neuromuscular conduction disease. It should not be used when there is an infection in the injected site and in children under 12 years of age.BTx-A is a category C drug and, therefore, should not be injected into pregnant or nursing women. 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 [31,32, 33]
Drug interactions have not been reported clinically, but 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 [33] The factors that increase the risks of producing neutralizing antibodies during BTx-A application include frequent BTx-A injection during a short period, high-dose injections, and increasing the dose of BTx-A injections. [5]

Conclusion

The role of botulinum toxin as a therapeutic agent for different medical conditions in oral and maxillofacial area is expanding. Botulinum toxin injection for the treatment of myofascial pain is a viable treatment option in the case of patients who do not respond to conservative treatment methods.The exact mode of action of BTx-A for pain relief has not been revealed completely and is multifactorial. Therapy with BTx-A is associated with a mild risk of adverse effects. Strict diagnostic criteria are required for further evaluation of

BTx-A injection regarding to efficacy for the different types of myofascial pain, bruxism, facial palsy, Frey's syndrome, migraine etc., and dose, intervals of application, cumulative effects of repeated injections and recommended postinjection therapeutic regimens. More clinical studies would be necessary to confirm the high level of scientific evidence of usage of BTx-A to determine its safety and efficacy in myofascial pain and other maxillofacial conditions.

References

1. Acquadro MA, Borodic GE. Treatment of myofascial pain with botulinum A toxin. Anesthesiology. 1994 Mar;80(3):705-6.
2. Carruthers JD, Carruthers JA. Treatment of glabellar frown lines with c. Botulinum-a exotoxin. J Dermatol Surg Oncol. 1992 Jan;18(1):17-21.
3. de-la-Hoz JL, de-Pedro M, Martín-Fontelles I, Mesa-Jimenez J, Chivato T, Bagües A. Efficacy of botulinum toxin type A in the management of masticatory myofascial pain: A retrospective clinical study. J Am Dent Assoc. 2021 Nov 8:S0002-8177(21)00478-5.
4. Binder WJ, Brin MF, Blitzer A, Schoenrock LD, Pogoda JM. Botulinum toxin type A (BOTOX) for treatment of migraine headaches: an open-label study. Otolaryngol Head Neck Surg. 2000 Dec;123(6):669-76. [PubMed]
5. Park KS, Lee CH, Lee JW. Use of a botulinum toxin A in dentistry and oral and maxillofacial surgery. J Dent Anesth Pain Med. 2016 Sep;16(3):151-157.
6. Pons M, Meyer C, Euvrard E, Weber E, Sigaux N, Louvrier A. MR-guided navigation for botulinum toxin injection in the lateral pterygoid muscle. First results in the treatment of temporomandibular joint disorders. J Stomatol Oral Maxillofac Surg. 2019 Jun;120(3):188-195.
7. Berry MG, Stanek JJ. Botulinum neurotoxin a: A review. J Plast Reconstr Aesthet Surg. 2012 Oct;65(10):1283-91.
8. Sipahi Calis A, Colakoglu Z, Gunbay S. The use of botulinum toxin-a in the treatment of muscular temporomandibular joint disorders. J Stomatol Oral Maxillofac Surg. 2019 Sep;120(4):322-325.
9. Malgorzata P, Piotr C, Edward K. The Mechanism of the Beneficial Effect of Botulinum Toxin Type a Used in the Treatment of Temporomandibular Joints Dysfunction. Mini Rev Med Chem. 2017; 17(5):445-450.
10. Freund B, Schwartz M, Symington JM. The use of botulinum toxin for the treatment of temporomandibular disorders: preliminary findings. J Oral Maxillofac Surg. 1999 Aug;57(8):916-20.
11. Khawaja SN, Scrivani SJ, Holland N, Keith DA. Effectiveness, Safety, and Predictors of Response to Botulinum Toxin Type A in Refractory Masticatory Myalgia: A Retrospective Study. J Oral Maxillofac Surg. 2017 Nov;75(11):2307-2315.
12. Villa S, Raoul G, Machuron F, Ferri J, Nicot R. Improvement in quality of life after botulinum toxin injection for temporomandibular disorder. J Stomatol Oral Maxillofac Surg. 2019 Feb;120(1):2-6.
13. Klasser GD, Greene CS. Role of oral appliances in the management of sleep bruxism and temporomandibular disorders. Alpha Omegan. 2007;100(3):111-9.
14. Seok H, Kim SG. Correction of Malocclusion by Botulinum Neurotoxin Injection into Masticatory Muscles. Toxins (Basel). 2018 Jan 2;10(1):27.
15. Kwon KH, Shin KS, Yeon SH, Kwon DG. Application of botulinum toxin in maxillofacial field: Part III. Ancillary treatment for maxillofacial surgery and summary. Maxillofac Plast Reconstr Surg. 2019 Oct 24;41(1):45.
16. Kamanli A, Kaya A, Ardicoglu O, Ozgocmen S, Zengin FO, Bayik Y. Comparison of lidocaine injection, botulinum toxin injection, and dry needling to trigger points in myofascial pain syndrome. Rheumatol Int. 2005 Oct;25(8):604-11.
17. Porta M. A comparative trial of botulinum toxin type A and methylprednisolone for the treatment of myofascial pain syndrome and pain from chronic muscle spasm. Pain. 2000 Mar;85(1-2):101-5.

18. Pihut M, Ferendiuk E, Szewczyk M, Kasprzyk K, Wieckiewicz M. The efficiency of botulinum toxin type A for the treatment of masseter muscle pain in patients with temporomandibular joint dysfunction and tension-type headache. J Headache Pain. 2016; 17:29.
19. von Lindern JJ, Niederhagen B, Bergé S, Appel T. Type A botulinum toxin in the treatment of chronic facial pain associated with masticatory hyperactivity. J Oral Maxillofac Surg. 2003 Jul;61(7):774-8.
20. Patil S, Willett O, Thompkins T, Hermann R, Ramanathan S, Cornett EM, et al. Botulinum Toxin: Pharmacology and Therapeutic Roles in Pain States. Curr Pain Headache Rep. 2016 Mar;20(3):15. [PubMed]
21. la Fleur P, Adams A. Botulinum Toxin for Temporomandibular Disorders: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines [Internet]. Ottawa (ON): CADTH. 2020 Feb 25.
22. Guarda-Nardini L, Manfredini D, Salamone M, Salmaso L, Tonello S, Ferronato G. Efficacy of botulinum toxin in treating myofascial pain in bruxers: a controlled placebo pilot study. Cranio. 2008 Apr;26(2):126-35. [Pubmed]
23. Kwon KH, Shin KS, Yeon SH, Kwon DG. Application of botulinum toxin in maxillofacial field: Part II. Wrinkle, intraoral ulcer, and cranio-maxillofacial pain. Maxillofac Plast Reconstr Surg. 2019 Oct 16;41(1):42.
24. Smith HS, Audette J, Royal MA. Botulinum toxin in pain management of soft tissue syndromes. Clin J Pain. 2002 Nov-Dec;18(6 Suppl):S147-54.
25. Awan KH. The therapeutic usage of botulinum toxin (Botox) in non-cosmetic head and neck conditions - An evidence based review. Saudi Pharm J. 2017 Jan;25(1):18-24
26. Drobik C, Laskawi R. Frey's syndrome: treatment with botulinum toxin. Acta Otolaryngol. 1995 May;115(3):459-61.
27. Gardner WJ, McCubin JW. Auriculotemporal syndrome; gustatory sweating due to misdirection of regenerated nerve fibers. J Am Med Assoc. 1956 Jan 28;160(4):272-7.
28. Hunt W, Joseph D, Newell R, Hanna HH. Gustatory sweating. Report of a case treated by tympanic neurectomy. Arch Otolaryngol. 1966 Mar;83(3):260-5.
29. Cooper L, Lui M, Nduka C. Botulinum toxin treatment for facial palsy: A systematic review. J Plast Reconstr Aesthet Surg. 2017 Jun;70(6):833-841.
30. Ahuja RB, Chatterjee P. Contemporary Solutions for the Treatment of Facial Nerve Paralysis. Plast Reconstr Surg. 2016 Feb;137(2):482e-483e.
31. Cote TR, Mohan AK, Polder JA, Walton MK, Braun MM. Botulinum toxin type a injections: Adverse events reported to the us food and drug administration in therapeutic and cosmetic cases. J Am Acad Dermatol. 2005 Sep;53(3):407-15.
32. Sipahi Calis A, Colakoglu Z, Gunbay S. The use of botulinum toxin-a in the treatment of muscular temporomandibular joint disorders. J Stomatol Oral Maxillofac Surg. 2019 Sep;120(4):322-325. [PubMed]
33. Kanbour A, Hurrell MJL, Ricciardo P. Velopharyngeal dysfunction following botulinum toxin type A injection to the lateral pterygoid muscles for recurrent jaw dislocation. BMJ Case Rep. 2021 Apr 22;14(4):e238766.

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