Application of Botulinum toxin Type A: An arsenal in dentistry

Lakshmana B Rao, Rajashekar Sangur, S Pradeep

ABSTRACT

An extremely effective way of preventing damage to and enhancing treatment of dental hard tissues and restorations would be to “de-programme” the muscles responsible for excessive destructive forces and other gnathological-related diseases. The new paradigm is the intramuscular injection of Botulinum toxin type A (BOTOX) into the affected muscles. It is a natural protein produced by anaerobic bacterium, Clostridium botulinum. The toxin inhibits the release of acetylcholine (ACH), a neurotransmitter responsible for the activation of muscle contraction and glandular secretion, and its administration results in reduction of tone in the injected muscle. There are seven distinct serotypes of Botulinum toxin, viz., A, B, C, D, E, F, and G, which differ in their potency, duration of action, and cellular target sites. This paper describes the different applications of BOTOX in dentistry.

Key words: Botulinum toxin type A, masticatory muscle hypertonicity, pharmaceutical splint, temporomandibular disorder

APPLICATIONS OF BOTOX IN DENTISTRY

BOTOX can be used in the following dental disorders:
- Temporomandibular disorder (TMD).
- Dental implants and surgery.
- Prominent gums.
- Masseteric hypertrophy.
- Mandibular spasm.
- Headache, migraine, and trigeminal neuralgia.
- Myofacial pain and neck pain.

TEMPOROMANDIBULAR DISORDER

TMD is an umbrella term used to describe a number of diseases affecting masticatory function, which may include
true pathology of the temporomandibular joint as well as masticatory muscle dysfunction. TMD manifests with facial pain, joint sounds, headache, periauricular pain, neck pain, and/or decreased joint excursions.\(^1\,^2\) Periodontal and occlusal diseases having an etiology in dysfunction of masticatory musculature are the key components of TMD. Muscular spasticity secondary to bruxism, external stresses, oromandibular dystonia, and psychomotor behaviors are common etiologic factors of TMD.\(^1\,^2\) Excessive pathologic nocturnal clenching (excessive centric grinding of teeth) of the jaw which in severe cases may manifest as dystonic bruxism, contributes to TMJ dysfunction in additions to damage to teeth, bone, joints, and gums. In untreated cases of excessive pathologic clenching or TMD, tooth decay is more prevalent because excessive forces can cause microfractures and abfracturing of enamel, especially around the existing restorations and may also be followed by gingival recession.\(^3\)

Bruxism (excessive eccentric grinding of teeth) can affect the muscles solely and/or lead to the formation of TMD causing joint damage. Chronic patients have headaches, bruxism-induced TMJ derangement or arthritis and difficulty in speaking, swallowing, or chewing. The symptoms are exacerbated by external factors such as fatigue, stress, and emotional extremes.\(^4\) If sleep bruxism is present, the most effective way to protect the teeth is with an occlusal appliance. The problem with occlusal covering appliances is that they do little or nothing to stop the bruxism and offer only a brief respite from headaches and bruxism-induced TMJ derangement or arthritis. In general, because of the numerous presentations of bruxism, the current treatments available are neither uniform nor universally successful.\(^1^2\,^4\)

Extra capsular TMD is often transient and usually the least invasive treatment options are considered best to commence the treatment. Many of the techniques currently in use are not ideal for all patients and muscular relaxation may pose a viable alternative. When muscle relaxants are used, the clenching reflex can be reduced or eliminated. A slight relaxation of muscle function reduces bruxing and is usually insufficient to affect chewing and swallowing.\(^5\) Prophylactic treatments for incipient TMD should be instituted for the reduction of both conscious and unconscious para-functional factors. Treatment of the myogenic component of TMD has been largely limited to supportive care. In more severe cases, physiotherapies, oral pharmacotherapy, biofeedback, and other treatment modalities usually provide short-term and inadequate relief. Chronic systemic pharmacotherapy is largely unsatisfactory because of the modest improvements and frequent side effects.\(^5\) Use of muscle relaxants like diazepam can curtail the activities of many patients. For patients who have failed with conventional treatment approaches, the least invasive method is the application of BOTOX injections into the painful masticatory muscles which can provide relief of intractable symptoms.\(^5\,^6\) Freund and Schwartz mentioned BOTOX as a muscle relaxant.\(^6\) Binder and colleagues while treating patients for facial lines with BOTOX injections, noted marked improvement of migraine symptoms in those who had failed to respond to conventional treatment.\(^3\,^7\)

**TREATMENT PROTOCOL FOR TMD**

The treatment begins with a lower dose, because it is always possible to titrate up to a higher dose, if necessary.

- The temporalis component of pain is treated with bilateral injections of 7.5 U into the anterior vertical fibers of each temporalis muscle. In more severe cases, 2.5 U are given into the middle and posterior third of the temporalis muscles. Pain relief for the tendon of temporalis is achieved with multiple injections of 2.5 U equidistantly spaced in the temple area outside the orbital rim.
- The masseter component of pain is treated with 5 U injected into the belly of the masseter below an imaginary line joining the tragus of the ear and the corner of the mouth.\(^8\)

There are several case reports, which are supporting the efficacy of BOTOX treatment for TMD:

- Freund et al. conducted a large open-label trial with 46 patients suffering from TMD and found that 150 U injections of BOTOX to the temporalis and masseter muscles significantly decreased pain and tenderness and improved function and mouth opening.\(^6\)
- Tan and Jankovic conducted a long-term open-label trial on 18 patients with a history of severe bruxism. Injections of BOTOX given to the masseter muscle (mean dose: 61.7 U/side; range 25–100 U), yielded a total duration of therapeutic response of 19 weeks.\(^9\)
- Lee et al. conducted a small open-label trial study to evaluate the effect of BOTOX on pain in six patients with limited mouth opening due to TMD. All patients showed clinical remission of pain symptoms without any adverse effects during the 5–12 months follow-up period.\(^10\)

**DENTAL IMPLANTS AND SURGERY**

Implant patients will benefit from pre-surgical BOTOX treatment. After multiple implants or when immediate loaded implants are placed, osseo-integration can be impeded by excessive functional forces in patients with para-functional habits. Overloading of the implants results in implant failure by loosening of the implant components or prevention of osseo-integration. The muscular relaxation achieved with prophylactic use of BOTOX injections to the masticatory muscles can be beneficial by allowing implant structures better osseo-integrated. Maxillofacial fracture repair often requires multiple fixation sites and hardware to overcome the strong forces of masticatory musculature. Overloading of these muscles can prevent fracture callus.
formation. The muscular relaxation achieved with prophylactic use of BOTOX injections to the masticatory muscles can be beneficial by allowing fracture healing in a more stable environment.\textsuperscript{[11-13]}

Excessive forces created by para-functional clenching impede healing and reattachment of gums and bone in the mouth following trauma. Low doses of BOTOX can potentially limit the para-functional clenching and its intensity and thus allow traumatized tissues to heal. High doses can be used as a "pharmaceutical splint," limiting muscle contraction before resetting and during rehabilitation after fracture of the facial bone, e.g., fractured mandibular condyle.\textsuperscript{[1]} Because para-functional clenching contributes to periodontal trauma, limiting clenching before and after periodontal surgery can benefit in healing. The use of a splint is often contraindicated because the teeth should be functional during healing. With significant bone loss, excessive forces may jeopardize dental stability and contribute to additional tooth loosening. The same applies in a patient with bone loss associated with either advanced periodontal disease or osteoporosis and a strong bite. Bite force is not diminished with reduced alveolar bone support. The use of BOTOX may offer an alternative to conventional splint therapy.\textsuperscript{[1,2]}

Kayikvioğlu and colleagues conducted a small open-label study to prospectively examine the use of BOTOX in five patients as an adjunct to zygomatic fracture fixation surgery, in an attempt to reduce the number of fixation sites and to prevent dislocation of the zygomatic bone. Preoperatively 100 U of BOTOX was injected into the masseter muscle of the fractured side. After 12–48 h of injection, patients were operated and muscle denervation was confirmed by EMG. The temporary paralysis of the masseter muscle allowed for fewer miniplates and/or microplates inserted among the patients and resulted in no complications. The Kayikvioğlu group also found similar benefits of adjunct BOTOX treatment for surgical reduction of mandibular condylar bone fractures.\textsuperscript{[13]}

**PROMINENT GUMS**

The display of excessive gingival tissue in the maxilla upon smiling or the “gummy smile” is both an oral hygiene and aesthetic issue with no simple remedy. Several surgical techniques have been reported in the literature for the correction of hyper-functional upper lip elevator muscles, such as (a) Rubinstein and Kostianovsky, (b) Miskinyar (c) Rees and LaTrenta techniques. However, they are not routinely used to treat gummy smiles. In general, the most common surgical corrections currently used are the LeFort I maxillary osteotomies with impaction for skeletal vertical maxillary excess and gingivectomies for delayed passive dental eruption with excessive gingival display. Excessive gum exposure is frequently attributable to over contraction of the upper lip muscles, particularly the levator labii superioris alaeque nasi. When this is the case, a less invasive approach is to limit muscular over-contraction. If applied in small, carefully titrated doses, these muscles can be proportionately weakened with BOTOX, which will reduce exposure of the upper gums when smiling. Polo conducted a study in which five patients with excessive gingival display due to hyper-functional upper lip elevator muscles were treated with BOTOX under electromyographic guidance. Patients received one 0.25 U injection per muscle bilaterally into the levator labii superioris, superioris labii alaeque nasi, and at the overlap areas of the levator labii superioris and zygomaticus minor muscles. All the patients were pleased with the results and the effective increase in upper lip length upon smiling averaged 124.2% and the duration of effect ranged from 3 to 6 months and no adverse effects were reported or observed.\textsuperscript{[14]}

**MASSETERIC HYPERTROPHY**

Patients who are chronic jaw clenchers frequently present with masseteric hypertrophy.\textsuperscript{[15]} The increased size of these muscles is evident in the patient’s facial appearance, which is often altered, e.g., the jaw can appear swollen and misshapen. To treat this, surgical resection was commonly resorted to which often resulted in substantial contracture. In several small but well-documented clinical trials by (1) Al-Ahmad, Al-Qudah,\textsuperscript{[16]} (2) Mandel and Tharakan,\textsuperscript{[17]} and (3) Rijsdijk and Vanes,\textsuperscript{[18]} injection of small aliquots of BOTOX into the masseter muscles resulted in a sustained reduction of masseter hyperactivity.

**MANDIBULAR SPASM**

It is a condition when the mandibular closing musculature remains semi-contracted or in spasm, resulting in restricted mouth opening. This type of muscular spasm limits completing the basic oral hygiene necessary to prevent oral disease and places restrictions on dental treatment. BOTOX treatment to the masticatory musculature diminishes the effects of hyper-functional or spastic muscles, that can significantly improve function and mouth opening, and effectively decrease pain and tenderness to palpation.\textsuperscript{[1-3]} Several case reports have been published, describing the effectiveness of BOTOX in patients with hemi-masticatory spasm, which include studies conducted by (1) Cersosimo et al.,\textsuperscript{[19]} (2) Auger et al.,\textsuperscript{[20]} (3) Kim et al.,\textsuperscript{[21]} and (4) Kim et al.,\textsuperscript{[22]} where all the patients responded positively to BOTOX injections.

**HEADACHE, MIGRAINE, AND TRIGEMINAL NEURALGIA**

Standard medications used in the treatment of headache and
migraine causes a number of side effects, such as stomach upset, drowsiness, and weight gain. Such side effects for BOTOX treatment are relatively rare. BOTOX 25–75 U injected into pericranial muscles relieves headache by relaxing the over active muscles by blocking nerve impulses that trigger contractions. For migraines, there is no muscle component involved. It is believed that BOTOX works by blocking the protein that carries the message of pain to the brain and relief typically takes effect in 2–3 weeks after injection. The longer the treatment duration, the better the pain relief.[2,23] According to Elcio, excruciating pain associated with inflammation of the trigeminal nerve of the head and face can be substantially relieved by injections of BOTOX.[24] According to Lawrence Robbins, BOTOX actually is an anti-inflammatory substance, decreasing, or antagonizing the inflammatory (neuronal/brain) effects of W (Calcitonin gene-related peptide).[25]

MYOFACIAL PAIN AND NECK PAIN

The etiology of myofacial pain syndrome is incompletely understood. Some clinicians believe that it characteristically results from either an acute episode of muscle overload or from chronic and/or repetitive muscle overload. Active myofacial trigger points, which cause pain, exhibit marked localized tenderness and often refer pain to distant sites and disturb motor function. Injection of muscles with BOTOX has been reported to be effective for myofacial pain caused by trigger points.[26]

Jennifer Warner, reported pain relief in 25 patients with chronic neck pain, after a single injection of Botox delivered to the affected neck muscle combined with standard physiotherapy.[27]

OTHER USES OF BOTOX

• The conventional treatment of ranula is surgical procedure. However, an innovative therapy with BOTOX is minimally invasive and the ranula gets resolved with minimal complications.[28]
• Recurrent dislocation of the mandibular condyle poses a difficult problem for affected patients. In the course of time, dislocations often become more frequent and more difficult to avoid. Even with good patient compliance, conservative treatment is often not sufficient. Operative procedures have also been described for the treatment of temporomandibular joint dislocation. On the other hand, BOTOX injections into the lateral pterygoid muscles offer the option of a predictable and prolonged period without renewed dislocation.[29]
• Facial aesthetics: The use of BOTOX in facial aesthetics for the treatment of wrinkles has recently become more popular as an alternative to surgical techniques.[30]
• Habitual clenches are more prone to snoring and sleep apnea. When BOTOX is injected into the masticatory muscles that hold the jaw in a retruded position, it enables the patient’s jaw to move slightly forward during sleep. This opens the air way sufficiently to reduce snoring.[2]
• Diagnostic application of BOTOX can be used to verify whether the correct diagnosis has been established or not. The pain originating from the pulp will not be relieved when BOTOX is injected into the muscles. Hence, the patients will be certain about the muscular or pulpal origin of the toothache. The diagnostic applications are limited only for the elimination of pain originating from muscles and the pain originating from other structures are not relieved and can be clearly differentiated.[3]

LIMITATION OF BOTOX

The therapeutic approach using BOTOX inhibits masticatory function temporarily and the masticatory forces will eventually return to previous levels once the effect of the drug has subsided.

CONTRAINDICATIONS AND ADVERSE EVENTS

The relative contraindications include pregnancy, lactation, neuromuscular diseases (myasthenia gravis, Eton-Lambert syndrome), motor-neuron diseases, concurrent usage of amino glycosides and sensitivity to toxin. The potential adverse effects of Botulinum toxin in oromandibular disorders include facial nerve palsy, pain at the injection site, flu-like symptoms, non-targeted muscle weakness, dysphagia, and hematoma. These complications are generally transient and resolve within a couple of weeks.[17]

PATIENT SELECTION

BOTOX therapy is appropriate for patients in whom other preventive treatments and medications are poorly tolerated or contraindicated, patients who are refractory to other treatments, special patient populations, and patients who simply prefer this treatment.[2]

DISCUSSION

BOTOX produces partial chemical denervation of the muscle resulting in localized reduction in muscle activity. BOTOX can be used as a sole therapy or as an adjunct to oral medication. Adding 4 ml of 0.9% preservative-free normal saline solution makes injections and the preparation should be used within 4 h. The potency of BOTOX is expressed as mouse units. A unit of BOTOX is defined as the LD50 for a colony of 20 gm Swiss-Webster mice,[31] extrapolated to the 70 kg human and each 0.1 ml contain 2.5 U of BOTOX. It is dispensed in small vials containing 100 U or 500 U. The
Botulinum toxin type A is marketed worldwide under the name BOTOX (Allergan, Inc. Irvine, CA, USA) and in Europe as Dysport (SpeyWood Pharmaceuticals Ltd., Maidenhead, UK). Another Botulinum toxin type A from Germany called Xeomin is also available. It is equipotent in BOTOX but does not have to be refrigerated and has no complexing proteins (theoretically reduced risk for developing antibodies) that would prevent it from working effectively. The FDA approved Botulinum toxin type B for the treatment of cervical dystonia is marketed under the trade name “Myobloc” (Elan pharmaceuticals) in USA and “NeuroBloc” (Solstice Neurosciences, Inc.) in Europe.

**CONCLUSION**

It is evident that the use of Botulinum toxin in the dental profession has a great potential. BOTOX paralyzes or weakens the injected muscle but leaves the other muscles unaffected. The injections block the extra muscular contractions but leave enough strength for normal use. Intra muscular injections of BOTOX re-establishes the balance between masticatory closing and opening muscles. Its use relieves muscle pain, reverses masseteric hypertrophy with improvement of facial outlines, and restores normal kinetics of TMJ.


Source of Support: Nil, Conflict of Interest: None declared.