Botox – the magical spell of dentistry: A literature review

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Abstract
Botox (botulinum toxin-BTX or botulinum neuro toxin) is a highly versatile multi-purpose therapeutic agent in the modern era, which is often used for cosmetic treatment of the face, for correcting lines and wrinkles, strabismus, blepharospasm, cervical dystonia, hyperhidrosis, torticollis, spasmodic dysphonia etc. It is also helpful in the management of muscle generated dental disorders. To review the relevant data accounting for the effects that botulinum toxin had on patients with muscular and dental disorders, a Medline/PubMed® literature search that only included articles published in English language from 1990 to June 2017 was done. A detailed discussion on the mechanism of action, clinical applications, treatment efficacy, adverse effects and contra indications are illustrated in this paper.

Key words: Botox, botulinum toxin, muscular disorders

Introduction
Botox (botulinum toxin-BTX or botulinum neuro toxin) is a protease exotoxin released by Clostridium botulinum, which is a gram-positive, rod-shaped, anaerobic, spore-forming, motile bacterium. It has a long history of therapeutic and cosmetic use. It has emerged as one of the safest and potent biologic toxin, with exceptionally high therapeutic results in modern medicine.1 Botox is famous for its minimally invasive reversible treatment modality. The Dental Quality Assurance Commission (DQAC) of Washington, New Jersey state board and Michigan board of dentistry have approved the use of botox and dermal fillers by dentists.2

Botulism was originally known as sausage poisoning because its outbreak was noticed after ingestion of poorly prepared blood sausages. In 1817, medical officer Christian Andreas Justinus Kerner was the first to describe the life threatening disease, botulism, which was caused by botulinum toxin, extracted from infected sausages.1,4 The term botulism was coined by John Muller in 1870, from the Latin word botulus meaning sausage. Clostridium botulinum, as a pathogen causing botulism, was first identified in Belgium, in 1897, by Prof Emile van Ermengem.1 In 1949, Arnold Burgen discovered that botulinum toxin blocks neuromuscular transmission. Botox was first used in medicine in 1980 to treat strabismus.4 Michael Kane, a plastic surgeon performed botulinum toxin injections to correct gummy smile since 1992.5 Since the inception of Botox ® cosmetics in 2002, with the approval of Food and Drug Administration (FDA), it has been widely used for cosmetic purposes also.2,6

Mechanism of action
Botulinum toxin brings about the degeneration of muscles or glands because of the blockage of release of acetylcholine (Ach) from the cholinergic nerve. The neurotransmitter Ach is responsible for initiating muscle contraction and glandular secretion. The docking proteins are essential for docking synaptic vesicles, carrying acetylcholine, to the presynaptic membrane (Figure 1). The endopeptidase activity of Botulinum toxin A enables the slicing of the membrane associated docking protein called “synaptosomal-associated

Figure 1: Neurotransmission

protein 25” (SNAP-25), which is a member of soluble N-ethylmaleimide sensitive factor attachment receptor protein (SNARE protein). The type B botulinum toxin cleaves synaptobrevin, found in the vesicular-associated membrane protein (VAMP). Thus, the cleavage of these docking proteins help botulinum toxin to block the transport of Ach vesicle to presynaptic membrane, which eventually affects the release of Ach on cholinergic nerve endings of motor nerves. The presynaptic block functionally denervates the muscles resulting in atrophy and a decrease in the bulk of the muscles. This results in a temporary reduction of muscle tone in the injected muscle which leads to flaccid paralysis for approximately 3 to 4 months and after which a repeat injection is advised. The neuromuscular transmission is re-established by regeneration of new axon terminals. The therapeutic effects of BTX A initially appears in the first 1-3 days, peaks by 1-4 weeks, and declines after 3-4 months. Due to this decline, it is advisable to administer botox injections 2-3 times a year, with a minimum gap of 3 months in between. This prevents the risk of the formation of the antibodies to protein, which prevents subsequent workups of botox.

Applications of botox in dentistry

**TMJ Disorders**

Temperomandibular joint (TMJ) disorders may be due to a myofascial or arthrogenic component, but majority of TMJ disorders have a myogenic component with muscular spasticity in relation to bruxism, excessive biting forces and external stressors. The conventional treatment modalities like intraoral appliances, occlusal adjustments, dental restoration, surgery, etc. may not withstand parafunctional forces continually. The muscular relaxation of muscles of the mastication with botulinum toxin A is an excellent alternative. For each of the temporalis muscles, at a concentration of 2.5–5.0 units per 0.1 mL botox is given, with an initial dosage of 10–25 units. Each masseter muscle need to be given 25–50 units each and the lateral pterygoids 7.5–10 units. For muscle relaxation only a small amount of masticatory force is required, which eventually reduces bruxism and clenching. It does not affect chewing and swallowing when administered in small quantities.

**Temporalis, Masseteric Hypertrophy and Bruxism**

In temporalis and masseter muscle hypertrophy cases, injections are given transcutaneously in the thickest part of the muscle. The patient is asked to clench his teeth and with the aid of Electromyography (EMG) localization, the site of injection is identified.

The masseteric hypertrophy as a result of chronic clenching can be treated with botox injection 25–50 U per side subcutaneously into the inferior border of the masseter, which results in relaxation. The botox injection helps in denervation of masseteric muscles. The more prominent hypertrophy yields the most impressive results. The maximum results are seen in the initial 1-2 months. Figure 2 shows the site of botox injection for masseteric hypertrophy.

Van Zandijke and Marchau were the pioneers to use botox for the successful treatment of severe bruxism.
in brain injured patients. They used 100 U of botulinum injection to the temporalis and masseteric muscles.\(^{11}\)

**Hemifacial and Mandibular spasm**

In hemifacial spasms, botulinum injections are given to the frontalis, corrugator supercilli, orbicularis oculi, zygomaticus major, buccinators and depressor anguli oris which gives relief for spasm. In the mandibular spasm cases, the mandible closing muscles remains semi-contracted or in spasm, which results in a limited opening of the mouth. The hyper functional and spastic muscles are relieved by botulinum injections.\(^{15}\)

**Gummy Smile**

Excessive gum exposure is mostly due to overcontraction/hyperfunction of upper lip muscles, namely levator labii superioris alaeque nasi, levator labii superioris, levator anguli oris, orbicularis oris, zygomaticus major and minor and risorius. The zygomaticus muscles are the major muscles causing the lifting of the upper lip and therefore influence gummy smile. The botulinum injections in small titrated doses helps to limit over contraction of upper lip muscles, thus minimizing the exposure of teeth while smiling. Woo Sang Hwang et al, proposed a 3 U botulinum injection at Yonsei point, a point located at the centre of a triangle formed by levator labii superioris alaeque nasi, levator labii superioris and zygomaticus minor (the three main lip elevator muscles) (Figure 3).\(^{16}\)

**Asymmetric smile**

Botox injections to overactive muscle fibers of depressor labi inferioris causes a gentle relaxation, thus helping in adjusting the smile. In bilateral cases, the hyperkinetic side is given a higher dose of botulinum injections. The drooping of the corner of the mouth is mainly due to hyper activation of depressor anguli oris. This hyperactivity can be treated with a single dose of injection of approximately 2-5 U (Botox\(^\text{®}\) and Xeomin\(^\text{®}\)) or 6-15 U (Dysport\(^\text{®}\)) on each side.\(^{17}\)

**Blepharospasm**

Blepharospasm is a condition characterized by an uncontrolled spasmic contraction of the orbicularis muscles of the eye, that lasts for seconds to minutes and in severe cases the eyes may remain closed for several hours. A 7 U botulinum injection given superficially to the orbicularis oculi, corrugator and procerus muscle helps reduce this condition.\(^{18}\)

**Trigeminal Neuralgia, head ache, migraine, other myofascial pains**

Headache can be relieved by injecting 25-100 U of botulinum injection into the overactive pericranial muscles and acts by blocking nerve impulses that trigger contractions.\(^{19}\) The type of headache, severity of symptoms and body size need to be considered prior to customizing the total dose.\(^{20}\)

**Sialorrhea**

Botox when injected to salivary glands like parotid and submandibular, blocks the release of Ach choline, thereby blocking cholinergic parasympathetic secretomotor fibers of salivary gland. This results in a decrease in salivary secretion. Each parotid gland is injected with 25-60 U of botulinum per treatment divided into 4 doses, as the gland has 4 quadrants, each of which receives 15 U of botulinum. The injections should be done under ultrasound guidance, into the body of the gland. The submandibular gland is injected by 10-40 U of botulinum divided into 2 doses of not more than 20 U. These injections should be into the parenchyma of the gland. At least 1cm distance should be maintained between each injections.\(^{21}\) Botox is also used in achalasia, hyperhidrosis, gustatory sweating (Frey syndrome) and salivary fistula. The injection in the proximity of the parotid results in decrease of salivary secretions, which causes glandular atrophy, thereby leading to the healing of the salivary fistula.\(^{22}\)
Surgical, orthodontic and Implantology purposes
The excessive force due to parafunctional clenching causes periodontal trauma, delay in healing of gongiva, bone etc. after trauma. The relief produced by the botox injection is really a boon in such post traumatic, post-operative cases.

The temporary paralysis of masseter muscles by 100 U botox injection helps in easier mini plate insertions in zygomatic fracture surgery cases. It also limits muscle contraction before resetting and rehabilitation, following facial bone fracture.

In post-traumatic splinting cases, the teeth should be functional during healing. Here, the botulinum toxin act as a pharmaceutical splint.

The patients prefer to look good in both static and dynamic facial expression. The soft tissue problems of orthodontically treated patients can be solved by botox injection, which ultimately offers the patient the best facial expression. If vertical component of muscular force is greater than force of fixed or removable appliance, then orthodontic treatments on clenching/deep/crossed bite patients gets prolonged. Botox reduces the treatment time in such cases. Botox also prevents relapse of orthodontic treatment which is caused by stronger muscle activity.

The muscular relaxation of masticatory muscles attained by botox injection allows implants for better osseointegration and fracture healing in a more stable environment. The spastic muscles generally cause delay in osseointegration and callus formation.

Other uses
In the decreased vertical dimension of new denture wearers, botox helps in retraining muscle. In mandibular dislocation cases botox injections are given to the lateral pterygoid muscle. It is also used in diagnostic purposes, in order to differentiate whether the pain is of muscular origin or due to any other etiology. It also helps in treatment of improving facial aesthetics. The list of adverse effects and contra indications are listed in Table 1 and 2.

Table 1: Adverse effects caused by botulinum toxin injection
- Allergic reactions
- Mild oedema and erythema
- Stinging or burning pain
- Transient numbness around injection site
- Facial nerve palsy
- Flulike symptoms
- Non targeted muscle weakness leading to masticatory difficulties, dysphagia
- If masseter muscle injection is given very close to the zygomatic arch, it may cause facial asymmetry and if it is close to orbit in temporalis injection may lead to blepharoptosis, diplopia and ptosis.
- With multiple sessions some patients may develop drug tolerance
- Risk due to needle puncture like bruising, local tenderness

Table 2: Contra indications for botulinum toxin injection
- Pregnancy (BTX-category C drug) and lactation
- Hypersensitivity to any components of BTXA or BTXB (i.e. BTX, human albumin, saline, lactose and sodium succinate)
- Any acute infection or inflammation on proposed site of injection
- Patients suffering from chronic degenerative neuromuscular disorder like myasthenia gravis, Eaton Lambert syndrome, amyotrophic lateral sclerosis, muscular dystrophy, multiple sclerosis.
- Psychologically unstable patients
- Taking certain medications that interfere with neuromuscular impulse transmission and potentiate effects of BTX (e.g. aminoglycosides, penicillamine, quinine, calcium channel blockers).

Discussion
Botox (botulinum toxin) is a protein and neurotoxin derived from bacterium Clostridium botulinum under anaerobic conditions. It is considered to be a very powerful neurotoxin with 7 botulinum serotypes (A, B, C, D, E, F, G). Among these, only purified exotoxins of botox type A (BTA) and type B (BTB) are available commercially. Injecting hyperactive muscles with minute quantities of botox type A helps to decrease the muscle activity (Table 3). Commercially, botulinum toxin A is available as Botox (onabotulinumtoxinA), Dysport (abobotulinumtoxinA), Prosigne, Xeomin (incobotulinumtoxinA) etc. and botulinum toxin B is available as myobloc (RimabotulinumtoxinB), neurobloc etc. About 20–25 units of botox is equal to 80 units of Dysport. Botox is marketed as sterile 50 units, 100 Units or 200 Units vacuum-dried powder.
It is a freeze dried powder that clumps at the bottom of the vial and is stored at a temperature of 2-4 °C. Each 100 units/vial contains Clostridium botulinum type A neurotoxin complex, 0.5 milligrams of human albumin, 0.9 milligrams of Nacl. 4.0 ml of 0.9% preservative free normal saline solution added to 100 U of vacuum-dried botulinum type A neurotoxin complex to make a solution, resulting in a 2.5 U/0.1 ml dose. While reconstituting the solution, rubber seal on the vial should be wiped with an alcohol swab and then a 5 ml, 25-guage needle syringe can be used to inject the required volume of normal preservative-free saline. 1ml tuberculin or insulin syringes are best suited for this purpose as they gauge the dose accurately in minute quantities. Once the solution is prepared it should be used within 4 hours. Any kind of shaking of the solution during transportation leads to frothing, which may cause surface denaturion of toxin and reduces duration of action, and hence should be avoided. Therefore, only freshly prepared solutions are generally used for procedures. The general guidelines for botox injection are listed in Table 4.

**Table 3: Disease conditions and various sites of injection with botox injection dosage**

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Site of injection</th>
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<tbody>
<tr>
<td>Trigeminal neuralgia, headache, migraine</td>
<td>25-100 U into pericranial muscle.</td>
</tr>
<tr>
<td>Masseteric muscle hypertrophy</td>
<td>25-50 U per side.</td>
</tr>
<tr>
<td>Gummy smile</td>
<td>3 U at Yonsei point on each side.</td>
</tr>
<tr>
<td>Drooping of corner of mouth</td>
<td>Bilateral injection of 2-5 U of botox given on trajectory of nasolabial fold to jaw line.</td>
</tr>
<tr>
<td>Tempo poro mandibular joint disorders</td>
<td>For temporalis and masseter–25 to 150 U IM (starting dose-temporalis 10 to 25 U, masseter 25–50 U, lateral pterygoid 7.5 to 10 U)</td>
</tr>
<tr>
<td>Bruxism</td>
<td>25-100 U per side into masseter muscle</td>
</tr>
<tr>
<td>Sialorrhea (drooling of saliva)</td>
<td>• 25–60 U injection to parotid, fractionated to 4 doses • 10–40 injected to submandibular gland, fractionated to 2 doses.</td>
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**Table 4: Guidelines to be followed while giving botox injections**

- Topical anesthetic cream should be applied on area of injection
- Always start with a lower dose of botox injection
- Muscles should not be paralyzed completely
- Males generally require higher dose due to larger muscle masses
- Depending on target muscle, injection dose can be varied between 10–50 U of botox per site (a total of 200 U in the masticatory system).
- Maximum of 400 U can be used if other sites in head and neck are included in protocol.
- Injection always done under guidance of electromyography (EMG) using a 27-gauge monopolar electrode injection needle.
- Identification of lateral pterygoid muscle is done intraorally with the EMG needle placed between pterygoid plate and coronoid process of the mandible

**Conclusion**

Botox injections are minimally invasive treatment modality with higher therapeutic results. These are helpful in the management of muscle generated disorders like TMJ disorders, muscular hypertrophy, spasms, myofascial pain dysfunction syndrome and so on. These injections are considered to be a real boon to the modern medical and dental field.

**References**