

Beyond Aesthetics: Botox in Dentistry- A Literature Review

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Abstract: Botox is primarily considered as a cosmetic treatment for lines and wrinkles on the face, but the botulinum toxin that Botox is derived from has a long history of therapeutic uses such as in cervical dystonia, hyperhidrosis, strabismus and blepharospasm. Now, as dental professionals it's high time we think out of the box and introduce the miracles of Botox into our field, taking into consideration the therapeutic uses it has in the treatment of certain oral conditions. The purpose of this article is to review the general information of botulinum toxin—especially in the field of dentistry—its mechanism of action, uses, contraindications and side effects. A search of Medline and Pubmed databases were performed targeting papers in English on the topic Botox in dentistry between 1976-2018, aiming at recognizing the therapeutic effects Botox has in treating oral conditions. Research and previous studies from a total of 63 articles provided evidence that the neurotoxin Botox gave positive results in both the medical and dental field and indeed provides a justifiable alternative to other more invasive procedures and thus we as dental professionals should encourage its use for treatment. Further clinical studies and research are needed to achieve and gain more knowledge about the neurotoxin and its effects. With current evidences available a narrative review has been put forward.

Keywords- Botox, mechanism, uses, contradictions

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I. Introduction

“Mirror mirror on the wall ,who is the.....?” Since time immemorial a billion men and women would have looked at the mirror and asked themselves the same question .No answers were forthcoming, atleast not until 1987 ,when Dr Alan Scott ,the Canadian eye doctor figured out that his injections could erase wrinkles.^[1] Since then, the magic of Botox has transformed many lives..And yes,we as dentists are the perfect professionals to work with botox for treatments beyond aesthetics.

A smile involves more than just the teeth. The perioral tissues are areas that can contribute to making people appear older than they are. “Its just time to think outside the mouth”.

Surely the dentist is better prepared , better trained and has more experience in the perioral and facial arena than other specialities .

What is Botox?

Botox is derived from the latin word “Botulus” meaning sausage and botulinum was originally called “sausage poisoning” because it occurred after ingestion of poorly prepared blood sausage. It is a neurotoxin which is prepared from the bacterium Clostridium Botulinum. It was Justinus Kerner (1786-1862), who first conceived a therapeutic use of botulinum toxin and coined the name “Botox”.^[2] Clostridium botulinum was first identified in 1897, in Belgium, by Professor Emile van Ermengem. In the same year ,an antiserum for botulism was made.^[3]

In 1949, Burgen was the first to discover that the toxin was able to block neuromuscular transmission .^[4] Dr Alan Scott, an Ophthalmologist from the Smith-Kettlewell Eye Research Foundation performed the first clinical tests on humans in 1978. Dr Michael Kane ,a plastic surgeon has been performing Botulinum toxin injections for excessive gingival show since 1992. ^[5] Niamtu has been performing Botulinum toxin injections for excessive gingival show 1999. In 2005 Mario Polo used botulinum toxin for the treatment of gummy smile. Injection with botulinum toxin type A at preselected sites is a novel, cosmetically effective, minimally invasive alternative for temporary improvement of gummy smiles caused by hyperfunctional upper lip elevator muscles.^[6]

Scott et al proved this fact by experimentally administering the Type A strain in monkeys. In the year 2000, Botox was approved for use in treating cervical dystonia and 2 years later for the temporary improvement of moderate to severe frown lines between the eyebrows. Botox is a purified exotoxin of the anaerobic bacteria, Clostridium botulinum. Seven types of botox toxin have been isolated; but only 2 types type A and type B have been made commercially available .^[7] The FDA (USA) has approved botulinum type A for treatment of severe

neck muscle spasm, excessive axillary sweating, spasm of the eyelids and temporary improvement in the appearance of moderate to severe glabellar lines(wrinkles).^[8-10]Type B has approval mainly for cervical dystonia (spasm of neck muscles).

Mechanism of Action

The toxin acts by inhibiting the acetylcholine release at the neuromuscular junction thus causing muscle paralysis. It acts in the following steps. [6,12] Toxin binds to the nerve. It is then internalized into the nerve. It is then cleaved by internal proteolytic enzymes. The degradation by-products interfere with the normal process of vesicle fusion to the plasma membrane. Inhibition of the exocytosis of acetylcholine, leading to neuromuscular blocking effect [13] Decreases the hyperactivity of muscles. Recovery phase: nerve growth factor is secreted by the paralyzed muscle. This causes the formation of new accessory terminals from the affected pre synaptic axon which stimulates the formation of new neuromuscular junction. [14,15]

Preparation

Botox is prepared by laboratory fermentation of *Clostridium Botulinum*. It would undergo lysis and liberate the toxin into the culture. The toxin is harvested, purified, crystallized with chemical and human serum albumin which is used as a dilutant, lyophilized and then sealed and stored in vials.

Each vial contains 100 units of Botox

- 0.5 mg of human albumin
- 0.9 mg of sodium chloride in a sterile vacuum dried form without a preservative.^[16]

These ingredients are packed in a sterile dry form without any preservatives. Shelf life is 21 months when kept refrigerated. Preparations should be reconstituted with 1-5 ml of saline without preservatives just before use. This solution should be refrigerated at 2-8°C and used within 4 hours.^[17]

Application of botox in dentistry

Temporomandibular joint disorders TMD is a 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. [21,23] Periodontal and occlusal diseases having an etiology in dysfunction of masticatory musculature are the key components of TMD. [24] Bruxism can affect the muscles solely and / or lead to formation of TMD causing joint damage. Chronic patients have headaches, bruxism induced TMJ derangement or arthritis and difficulty in speaking, swallowing or chewing which are exacerbated by external forces such as fatigue, stress and emotional extremes. [25] Conventionally it is treated with intra-oral appliances, occlusal corrections, retraction surgery etc. But they are irreversible, expensive for majority of the patients. For such patients, Botox is preferred. 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. [26,27]

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.

Pain on Temporalis

- Bilateral injections 7.5 units into the anterior vertical fibers of each temporalis muscle
- In more severe cases - 2.5 U injected into middle and posterior third of the temporalis muscle.
- Pain relief for the tendon is achieved with multiple injections of 2.5 units equidistantly spaced in the temple area outside the orbital rim.

Pain on Masseter component

5 units of botox into the belly of the masseter muscle below an imaginary line joining the tragus of the ear and corner of the mouth.

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.^[28]
- 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 responded well.

- duration of therapeutic response of 19 weeks .^[29]
- Lee et al conducted a small open-label trial study to evaluate the effect of Botox on pain in 6 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 .^[30]

Diagnostic application

The diagnostic applications are limited only for the elimination of pain originating from the muscles, and the pain originating from the other structures are not relieved and can be clearly differentiated.^[51]

USES	INDICATION	MECHANISM OF ACTION	REFERENCES
<p>Ji</p> <p>DENTAL IMPLANTS AND SURGERY</p>	<p>After multiple implants or when immediate loaded implants are placed, osseo integration can be impeded by excessive functional forces in patients with parafunctional habits.</p> <p>Overloading of the implants results in implant failure by loosening of the implant components or prevention of osseo-integration.^[18-20]</p>	<p>The muscular relaxation achieved with prophylactic use of Botox to masticatory muscles can be beneficial, and also allows fracture healing in a more stable environment.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 .^[21]</p>	

<p>PROMINENT GUMS</p>	<p>Several surgical methods have been reported for the correction of hyperfunctional upper lip elevator muscles, such as (a) Rubinstein Kostianovsky,(b) Miskinyar(c) Rees and La Trenta techniques. However they are not routinely used to treat gummy smiles.In general ,the most common surgical corrections currently used aremaxillary osteotomieswith impaction for skeletalverticalmaxillary excessand gingivectomies</p> <p>for delayed passive dental eruption with excessive gingival display.</p> <p>Excessive gum exposure is attributed to over contraction of the upper lip, particularly levator labii superioris. When this is the case , a less invasive approach is to limit muscular over contraction.</p>	<p>If applied in small, carefully titrated doses these muscles can weakened with</p> <p>Botox, which will reduce exposure of the upper gums while smiling.</p>	<p>Polo conducted a study in which five patients with excessive gingival display due to hyperfunctional upper lip elevator muscles were treated with Botox under electromyographic</p> <p>guidance.Patients received one 0.25 U injection per muscle bilaterally into the levator labii superioris ,Superior labii alaque 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</p> <p>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.</p> <p>A safe and reproducible injection point for Botulinum toxin A around the converging area of the three muscles has been proposed and proved effective in clinical applications.Intramuscular injection for correction of excessive gingival display is given at “Yonse poing”.(Woo-Sang Hwang).Botulinum toxin A is diluted by adding 4 ml of 0.9% normal saline.</p>
<p>REMOVABLE PROSTHODONTI-CS</p>	<p>While it is true that more and more patients everyday are receiving implant treatment to help stabilize dentures, there will always be patients who cannot afford implant therapy or because of underlying challenges such as medical history or bone resorption, are not candidates for implant therapy</p>	<p>You will often see a hypertrophic masseter and can even feel strong lateral and medial pterygoid muscles that cause the difficulty in adjusting to removable prosthodontics.^[31] Muscle training with Botox may provide relief as dentists become more familiar with their use.</p>	
<p>MASSETERIC</p>	<p>Patients who are chronic jaw clencher frequently present with masseter hypertrophy. ^[32]The increased size of these muscles is evident in the patients facial appearance which is often substantially altered.The jaw appears swollen and out of shape.The common treatment before botulinum toxin was</p>	<p>In several small but well documented clinical trials,the injection of small aliquots(30 U per side) of botox into the masseter muscles resulted in a sustained reduction of masseter hyperactivity.^[26,27,32,34]</p> <p>Overtime,in most patients ,reduction</p>	

<p>HYPERTROPHY</p>	<p>surgical resection^[33],which results in substantial contracture.</p>	<p>in massetric hyperactivity has been found to yield a concomitant reduction in gross masseter size(maximum reduction 35.4%).If the underlying pathology responsible for the hyperactivity is resolved,the reduction in masseter hypertryophy remains an unduring effect even after Botox applications have ceased .^[27,34]</p>	
<p>OROMANDIBULAR DYSTONIA</p>	<p>It is a movement disorder characterized by involuntary spasms and muscle contractions.It manifests as distorted oral positions and function resulting in difficulty in speaking,swallowing and eating.^[35]</p>	<p>Botox was injected into the masseters and submental complex.Improvement in function for chewing and speaking was reported in 69.7% of the patients.</p>	<p>Most of the reported literature on OMD has been open-label studies,but all have reported improvement with botulinum toxin injections.^[36-40]</p> <p>The largest study to date was a prospective open-label conducted by Tan and Jankovic that treated 162 patients with OMD over a 10 year period ^[32].</p>
<p>MANDIBULAR SPASM</p>	<p>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 basicoralhygienenecessary to preventoral diseaseand placesrestrictions on dental treatments.^[41]</p>	<p>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.</p>	<p>Several cases have been published,describing the effectiveness of Botox in patients with hemi-masticatory spasm,which includes study conducted by (1) Cersosimo et al ^[42](2) Auger et al ^[43](3) Kim et al ^[44] (4) Kim et al ^[45], where all the patients responded positively to Botox injections.</p>
<p>TRIGEMINAL NEURALGIA</p>	<p>According to Elcio,excruciating pain associated with inflammation of the trigeminal nerve of thehead and facecan be substantially relieved by injections of Botox^[46]</p>	<p>According to Lawrence Robbins,Botox is an inflammatory substance,decreasing or antagonizing the inflammatory effects of calcitonin gene-related peptide. ^[47]</p>	
		<p>Botox blocks the release of acetylcholine at the cholinergic synapses of the autonomic nervous system,thus blocking the parasympathetic secretomotor fibers of the salivary gland.</p> <p>Hence botulinum toxin has been tested in some autonomic diseases</p>	<p>Lim and Choi ^[49] have reported that injection of botulinum type A is a highly effective and relatively safe primary method of treatment for an acute post parotidectomy salivary fistula.</p>

SIALORRHEA		like achalasia, hyperhidrosis and gustatory sweating (Freys syndrome) . ^[48]	
RETRAINING MUSCLES DURING ORTHODONTIC TREATMENT.		Botox can be used to prevent relapse of orthodontic treatment in case of patients with stronger muscle activity such as that of mentalis muscle. Botox can be used to reduce the intensity of the muscle post treatment and overtime, the muscle may be retrained to a more physiological movement.	
ENHANCING FACIAL ESTHETICS	The facial wrinkles can be treated with Botox. But, the pathogenesis of wrinkles should be known first.	The use of fillers in the lower face and the use of Botox in the upper face are advised. When the wrinkle is primarily caused by muscular action deforming the overlying skin, Botox can be an extremely effective treatment in the lower face. ^[50]	

Adverse Effects

- Adverse effects are of limited duration that are common, localized and not of a serious nature.
- Common with any percutaneous injection
- Mild stinging, burning or pain with injection.
- Edema around the injection site.
- Erythema around the injection site.
- Mild headache, localized and transient.^[52]

Rare and idiosyncratic

- Numbness and paresthesia (localized and transient)
- Focal tonic movements (twitching)
- Mild nausea and occasional vomiting
- Mild malaise and myalgias (localized and generalized)

Rare adverse effects of longer duration that can be serious and are not technique dependent

- Immediate hypersensitivity reactions
- Urticaria
- Dyspnea
- Soft tissue edema
- Anaphylaxis

It has been seen that masseter muscle paralysis induced by BoNTA leads to significant microanatomical changes by day 14, preceded by molecular changes as early as 2 days in bone, and 7 days in muscle. Therefore, masseter muscle atrophy and subchondral bone loss detected at 14 days are preceded by molecular responses that occur during the first week after BoNTA intervention.^[53]

Contraindications

- Patients should not be treated or treated with extreme caution who are
- Psychologically unstable or who have questionable motives and unrealistic expectations
- Dependent on intact facial movements and expressions for their livelihood
- Afflicted with neuromuscular disorder(e.g myasthenia gravis,Eaton-Lambert syndrome)
- Allergic to any of the components of BTX-A or BTX-B (i.e.BTX,human albumin,saline,lactoseand sodium succinate)
- Taking certain medications that can interfere with neuromuscular impulse transmission andpotentiate the effects of BTX (e.g aminoglycosides,penicillamine,quinine and calciumblockers).Pregnant or lactating (BTX s are classified as pregnancy category C drugs)^[54]

II. Conclusion

Botox produces partial chemical denervation of the muscle resulting in localized reduction in muscle activity.It can be used as a sole therapy or as adjunct to oral medication. Adding 4ml of 0.9% preservative-free normal saline makes injections and the preparations to be used within 4 hours. The potency of botox is expressed as mouse units.A unit of botox is defined as the LD 50 for a colony of 20gm Swiss Webster mice [45], extrpolated to the 70 kg human and each 0.1 ml contains 2.5 U of botox.It is dispensed in small vials containing 100 U or 500 U.The lethal dose of botox is estimated to be about 3000 U.The usual maximum dose recommended for dental applications at an injection session is about 80-100 U.It means 30 vials of Botox will have to be injected before a potentially lethal outcome. Before injecting Botox into the muscle /or joint/or skin ,the skin has to be cleaned with an alcohol/betadine/chlorhexidine swab. For muscle injections ,the site to be injected should be determined by using a small electric recorder or a larger machine called an EMG machine,which helps in correctly locating the area of the muscle to be injected.Ultrasound guided injections may also be used for deeper joints or muscles .Botox is injected using 1ml tuberculin syringe and 0.30 gauge half inch needle.[55] Injections of a small amount of this toxin into the muscle produces atrophy and weakens within 1-20 days and recovers over 2-4 months as new terminal axons sprout and restore transmission.[56] Injectionsarespaced outfor aminimumof 3 monthsto minimizetherisk of antibody formation to the protein ,which would prevent Botox from working for the subsequent time. Specialised equipment can be used for more accurate injections that include

- EMG guided injections (with NeuroMax 1004)
- Peripheral nerve stimulator (NS 272)
- Ultrasound guided injections (including the Canadian center for MSK ultrasound)
- MD injectors (Botox therapeutic).^[57]

Botulinum toxin type A is marketed worldwide under the name BOTOX (Allergan,Inc.Irvir,CA, USA) and in Europe as Dysport. [24,29]. Xeomin is also available which is equipotent to Botox but does not have to be refrigerated and has no complexing proteins 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”in USA and Neurobloc in Europe. Botulinum toxin A achieves close to immediate results in one short appointment ,but the results are not permanent and lasts for 6 months,with a range of 4-8 months.[58] The therapeutic effects of Botulinum toxin A first appear in 1 to 3 days,and peak in 1 to 4 weeks and declines after 3 to 4 months.[59] At the cellular level ,3 to 4 weeks after a single injection of Botulinum toxin A in mice,there is sprouting of new processes along the nerve axon,with formation of multiple synapses with the muscle and regulation of the muscle nicotinic receptors.Subsequently the neuronal sprouts undergo regression and the original synaptic connection is restored,with restoration of the original neuromuscular junction.[60,61] Results from experimental studies in animal models, makes it highly recommended for both clinicians and patients to consider the putative bone loss evoked by BoNTA-induced masseter muscle atrophy as a relevant factor prior to a treatment.[62] Therefore, the presented evidence suggests the importance of considering the need to develop follow-up protocols to permanently monitor the associated bone structure by proper imaging techniques after BoNTA intervention in the masseter muscle. [63]

Why should dentists offer Botox?

- Smile makeover expert
- More training and knowledge of oral and orofacial areas than any other health careprofessional
- Comprehensive knowledge of facial muscle expression
- Highly experienced with injections and aesthetic options
- Consideration of dental and facial proportions before augmentation for optimal results.
- Can offer quick and convenient treatment during routine dental visits.

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Conflict of interest

There are no conflicts of interest

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