Review Article

Botulinum Toxin: A Peek at a Wonder Drug for Dentistry
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Abstract: Botulinum toxin for therapeutic use has been available in India since 1994. The general perception of this “wonder drug” in the field is that its role is limited to esthetic and cosmetic enhancements. This review is an attempt to bring to light the true medical and specifically dental benefits of this deadly neurotoxin as a minimally invasive treatment option. Continuing research worldwide and the isolation of newer strains of Cl. Botulinum could place this once deadly neurotoxin in a key position for an even wider application of use in both medical and dental conditions in the near future. Keywords: Botox; Bruxism; Esthetics; Dystonia; Temporomandibular Joint Disorders.

INTRODUCTION

The Botulinum toxin is a neurotoxin produced by the bacterium Clostridium botulinum. It is the most potent naturally occurring toxin known, with as little as 30–100 ng being potentially fatal. Consumption of just a few milligrams of neurotoxin-containing food is likely to be sufficient to cause illness and potential death. It is responsible for botulism, a severe neuroparalytic disease that affects humans, animals, and birds [1,2]. Cl. botulinum is responsible for foodborne botulism, infant botulism, and wound botulism, adult infectious botulism and inadvertent botulism following botulinum toxin injection [3]. Cl. botulinum produces heat resistant endospores that are commonly found in soil and allow for survival in adverse conditions.

Clostridium botulinum was first recognized and isolated in 1895 by Emile van Ermengem following an incident of severe neuroparalytic illness that included three fatalities among 34 musicians in Belgium that year. He named the organism Bacillus Botulinus[4,5]. Justinus Kerner described botulinum toxin as a "sausage poison" and "fatty poison", because the bacterium caused poisoning by growing in improperly handled or prepared meat products [6,7,8]. Ida A. Bengston placed the organism into the genus Clostridium [9].

Since the second half of the 20th century research has been conducted into the use of botulinum toxins for clinical therapy[10,11,12].

Classification and Mechanism of Action of Botulinum Neurotoxin

Present day Cl. Botulinum are evolved forms of the organism isolated by van Ermengem[13]. Cl. Botulinumis classified into four phenotypes (I to IV). Botulinum neurotoxin production (BoNT) is the unifying characteristic of the phenotypes. There are eight types of BoNT. The most recent was described in January 2014,[14,15,16].

Structurally the BoNT is a non-covalently bound complex with two or more protein complexes which include a haemagglutinating proteins as well as a non-toxic non- haemagglutinating proteins. The non-toxic proteins enhance the toxin potency and stabilize the BoNT in the gastrointestinal tract.

The neurotoxin acts by preventing acetylcholine (ACh) release in the target muscles causing clinically visible muscle paralysis. Out of eight known BoNT serotypes, types A, B, E, F and H have been documented to cause Botulism in humans [13,15,16,17]. BoNT A has been shown to have the highest rate of mortality in humans[1,2,18].

Silver Linings - Clinical Applications of the Botulinum Toxin

Genetic sequencing of Cl. Botulinum and extensive studies on the BoNT have allowed its use in controlled dose to treat a variety of disorders utilizing the ability of the BoNT to produce muscle relaxation when administered in Controlled Titered Doses. Table-1 presents a summary of disorders where administration
of BoNT has been shown to have clinically successful results. [19,20,21,22,23,24,25,26].

Commercially only two serotypes of BoNT are used in the treatment of medical and dental conditions – BoNT/A (Onabotulinumtoxin A, Abobotulinumtoxin A and Incobotulinumtoxin A) and a BoNT/B (Rimabotulinumtoxin B) [14, 27, 28, 29, 30, 31]. The formulations are prepared using different processes which determined by different biological assays based on their clinical use. The potency of a single unit varies greatly among the commercial types. (Table II)

Therapeutic BoNT doses have to be adjusted according to multiple factors such as severity of the hyperactive muscle, number of muscles involved, age, and previous response to BoNT therapy. The duration of BoNT effect is variable depending upon the type of neurotoxin, dose, site of injections, and clinical applications. In the disease state, BoNT A has a longer paralysis than BoNT B; likewise, formulations of BoNT/A have shown to have a longer duration of action than BoNT/B formulations in muscle dystonia [32,33]. Both however have a similar duration of action when used in treating sialorrhea secondary to neurological diseases [34].

**Facial Esthetics**

The general public’s view of the use of “Botox®” is for correction and enhancement of esthetics. In terms of micro- (dental) esthetics, the use of BoNT/A finds its place in the correction of gummy smiles[35], lip augmentation [36], and reduction of facial wrinkles contributing to an overall improvement in a macro-esthetic treatment plan[37,38]. Correction of these conditions is brought about by a temporary paralysis of a specific muscle or muscles caused by the action of BoNT.

Gummy smiles due to hyper-functional upper lip elevator muscles when paralyzed by the BoNT/A, fall inward and downwards, reducing the amount of gingival display changing the smile type [39]. Results are generally noticeable in 2 weeks and last up to 3 to 6 months.

Only those facial wrinkles which are due to muscle contractions can be treated by BoNT therapy. Wrinkles due to degenerative processes are not treatable by BoNT therapy. Noticeable improvement is seen within 1 to 3 days after injection with maximum improvement seen in 1 to 2 weeks. Repeat injects may be carried out at this period during a review and the effects can last up to 8-12 weeks.

Complications following injection of botulinum neurotoxin for esthetic purposes are well documented and can range from bruising to severe life threatening conditions if not administered correctly[40,41].

**In the Management of Sialorrhea**

BoNT/A has been successfully used in the treatment of hypersalivation secondary to neurological and otolaryngologic conditions such as in infant cerebral palsy, Parkinson’s disease and amyotrophic lateral sclerosis, and oral cancers. Complications documented are dysphagia, xerostomia and chewing difficulties[22,42,43,44,45].

**In the Management of Temporomandibular Disorders (TMD), Oro-Fascial Pain and Oromandibular Dystonias**

Non-Surgical management of TMD, orofascial pain and oromandibular dystonias using BoNT has shown promising results due to its muscle relaxing properties [46,47]. BoNT/A therapy primarily targets the muscles of mastication. It is administered at multiple sites of the affected muscles depending on the amount of muscle tenderness and pain reported by the patient to achieve the desired clinical results [48].

Good outcome has been cited for the treatment of habitual dislocation of the TMJ-Joint secondary to neurological diseases with BoNT/A. Single doses have been shown to be satisfactory in treating the dislocations [49,50,51]. It has also been hypothesized that BoNT/A may be useful in preventing trauma induced TMJ ankylosis. Injection of BoNT/A into the lateral pterygoid muscle causes temporary immobilization of the TMJ and thus prevents the traumatic TMJ ankylosis [52].

Parafunctional habits of the jaws associated with muscle hypertrophy can be treated with BoNT/A injections [53,54]. Bruxism has been associated with neurological disorders and dystonias[55,56]. Single dose injections of BoNT/A have been reported to completely abolish severe bruxism behaviors. It is thought that jaw muscle paralysis induced by BoNT/A disrupts the feedback loop from the trigeminal motor nucleus and inhibits the central bruxism generator or may deactivate periodontal mechanoreceptors during mastication, which may have a facilitatory effect on jaw closure motoneurons[57].

**BoNT in the treatment of Tetanus**

Reports in literature show that Botulinum neurotoxin may be useful in treating Tetanus, if administered into the masseter and temporalis muscles early in the course of the disease to reduce the risk of pulmonary aspiration, involuntary tongue biting, anorexia allowing for dental care. [58].

Tetanus is caused by the toxin released by *Clostridium Tetani*. The tetanus toxin moves trans-synaptically into inhibitory nerve terminals, where vesicular release of inhibitory neurotransmitters becomes blocked, leading to disinhibition of lower motor neurons resulting in characteristic symptoms of the disease - muscle rigidity and spasms.
Botulinum toxins enter nerve terminals of lower motor neurons where toxins attack synaptic vesicle proteins differentially. Compared to tetanus toxin, the botulinum toxins undergo less axonal and trans-synaptic transport. Therefore, the effects of botulinum toxins remain fairly confined to the nerve terminals of lower motor neurons, inhibiting release of acetylcholine and activation of voluntary muscles[59,60,61]. This may be the reason why BoNT could have a role in reducing the muscular hyperactivity in Tetanus.

Administration into the trapezius, splenius capitis, levator scapulae and sternocleidomastoid muscles, which are also involved in tetanus should be avoided due to proximity to vital structures such as the carotid artery, during injection of the toxin and also to avoid possible spread of the BoNT effects to the larynx [58].

In Maxillo-facial Surgery
Correction of maxillofacial trauma usually requires multiple fixation sites and hardware to overcome strong forces of masticatory musculature. The muscular relaxation achieved with BoNT A injections to the masticatory muscles may be beneficial by allowing ease in operating and healing following fixation[62].

Contra-Indications and Complications of Botulinum Toxin Therapy

Currently available Botulinum Toxin formulations are safe and effective. Cited complications associated with the use these formulations are minor such as pain at the injection site, flu-like symptoms, non-targeted muscle weakness. Dysphagia and hematomas may occur though rare [37,63]. The adverse events associated with chronic, periodic exposure to BoNT type A or B injections are generally minor and self-limiting, and even decrease over time [64].

Are Dentists Allowed to Administer Botulinum Toxin as Part of Dental Therapy?
Different dental councils world over have varied policies regarding whether licensed dental surgeons should be allowed to administer botulinum toxin as part of dental therapy. The American Dental Association poses a neutral stand on the issue. Individual state councils in the USA have their own policies. Some states in the USA allow board certified oral and maxillofacial surgeons to practice BoNT therapy as training is included in their curriculum. General dentists and other specialists are allowed to practice only after completing accredited training programs and obtaining board certification[65,66].

Administration of BoNT for cosmetic procedures in settings other than a certified medical center is not allowed [67].

In India, there are currently no regulations regarding the use and administration of Therapeutic Botulinum Neurotoxin by dentists.

Table -1: Conditions for which treatment with botulinum toxin may be used [19-26]

<table>
<thead>
<tr>
<th>I. Cosmetic Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Muscular facial lines</td>
</tr>
<tr>
<td>b. Facial asymmetries</td>
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<tr>
<td>II. Dystonias</td>
</tr>
<tr>
<td>a. Bruxism</td>
</tr>
<tr>
<td>b. Oromandibular Dystonia (OMD)</td>
</tr>
<tr>
<td>c. Cervical Dystonia (CD)</td>
</tr>
<tr>
<td>d. Cranio-cervical Dystonia</td>
</tr>
<tr>
<td>e. Focal Hand Dystonia (FHD)</td>
</tr>
<tr>
<td>f. Hemifacial spasm</td>
</tr>
<tr>
<td>g. Tremors</td>
</tr>
<tr>
<td>h. Tics</td>
</tr>
<tr>
<td>i. Re-innervation Synkinesisas</td>
</tr>
<tr>
<td>j. Myokymia</td>
</tr>
<tr>
<td>k. Neuromytonia</td>
</tr>
<tr>
<td>l. Stiff Person Syndrome</td>
</tr>
<tr>
<td>III. Spasticity and Muscle Disorders</td>
</tr>
<tr>
<td>a. Masseteric hypertrophy</td>
</tr>
<tr>
<td>b. Mandibular spasm</td>
</tr>
<tr>
<td>c. Chronic low back pain</td>
</tr>
<tr>
<td>IV. Hypersecretory Disorders</td>
</tr>
<tr>
<td>a. Sialorrhea</td>
</tr>
<tr>
<td>b. Hyperhidrosis</td>
</tr>
<tr>
<td>c. Hyper-lacrimation</td>
</tr>
<tr>
<td>d. Rhinorrhea</td>
</tr>
<tr>
<td>V. Ophthalmic disorders</td>
</tr>
</tbody>
</table>

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a. Strabismus, Nystagmus
b. Exotropia, esotropia, entropium
c. Protective ptosis
d. Blepharospasm

VI. Pain
a. Temporomandibular Disorders (TMD)
b. Myofacial pain and neckpain
c. Trigeminal neuralgia
d. Tension headache
e. Migraine

VII. Pelvic floor and Gastrointestinal disorders
a. Achalasia
b. Anal fissures
c. Detrusor-Sphincter Dyssynergia
d. Vesicle sphincter spasm
e. Sphincter Odii spasm
f. Anismus
g. Vaginismus

VIII. Lower urinary tract disorders
IX. Miscellaneous
a. Wound healing and diabetic neuropathy
b. Eyelid opening
c. Tetanus
d. Stuttering
e. Perioperative fixations in orthopedic surgeries.
f. Facial Trauma and Reconstructive surgery
g. Non-Surgical Correction Gummy Smiles

Table 2: Commercially Available Botulinum Toxin Formulations

<table>
<thead>
<tr>
<th>Contents</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Presentation</th>
<th>Available in India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clostridium Botulinum Type A</td>
<td>BOTOX® (Onabotulinumtoxin A)</td>
<td>Allergan India Private Ltd.</td>
<td>Powder for Injection 50 IU x 1's 100 IU x 1's</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>NEURONOX® (Onabotulinumtoxin A)</td>
<td>Ranbaxy Laboratories Ltd.</td>
<td>Powder for Injection 100 IU x 1's</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>DYSPORT® (Abobotulinumtoxin A)</td>
<td>Ipsen Biopharm Ltd.</td>
<td>Powder for Injection 300 IU x 1's 500 IU x 1's</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>XEOMIN® (Incobotulinumtoxin A)</td>
<td>Merz Pharma GmbH &amp; Co KGaA</td>
<td>Powder for Injection 50 IU x 1's 100 IU x 1's</td>
<td>No</td>
</tr>
<tr>
<td>Clostridium Botulinum Type B</td>
<td>MYOBLOC® (Rimabotulinumtoxin B)</td>
<td>Solstice Neurosciences</td>
<td>Powder for Injection 2,500 Units/0.5 mL 5,000 Units/1 mL 10,000 Units/2 mL</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>NEUROBLOC® (Rimabotulinumtoxin B)</td>
<td>Eisai Europe Ltd.</td>
<td>Powder for Injection</td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSION
Botulinum toxin therapy is a safe and promising option for patients suffering from a variety of dental conditions and esthetic concerns. It is a minimally invasive option that will ease operative procedures, enhance patient satisfaction and treatment results. Minimal post-operative complications occur provided basic procedural guidelines are followed – individualized doses to the patients based on muscle size, pain and activity, injecting the toxin into established tender muscle points, using the smallest needle size possible, use of adjunctive topical local anesthesia and monitoring of EMG activity during further associated procedures.

The isolation of newer strains of Cl. Botulinum and continuing research worldwide could place this once deadly neurotoxin in a key position for an even wider application in both medicine and dentistry. Current costs of the drug restrict its use to a minority of...
the patients who would benefit from its therapeutic
advantages. A need for research and production of
the drug in India is paramount if it has to be made viable
for therapeutic use in our country.

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