Review Article

Botoxonomics: A Palliative Prick

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Abstract

In the present century, botulinum toxins (BTs) have gone from the deadly poison to remarkably versatile therapeutic agent. Botulinum is derived from the Latin word "botulus," meaning sausage, and botulism was originally called "sausage poisoning" because it occurred after ingestion of poorly prepared blood sausage. It works by inhibiting the release of acetylcholine at neuromuscular junction interrupting the contraction process of the muscles and causes a temporary paralysis. Blockade is temporary, after which there is a return of neuromuscular function. BT can be used for the treatment of temporomandibular disorders, bruxism, correction of a gummy smile, black triangle and it can also be used to relieve patients with facial pain, including treating trigger points. Indications of botulinum for oral and maxillofacial esthetics are to improve dental lip lines and smile lines. Other cosmetic indications are crow feet, eye hooding, hyperhidrosis, glabellar lines, etc. The benefits of this toxin have made a sensation for the artists and celebrities along with common people nowadays. Although it has a few adverse effects, it has generally proven to be therapeutic and safe.

Keywords: Aesthetics dentistry, Botolinum toxin, Treatment

INTRODUCTION

Botulinum toxin (BT) is a protein and neurotoxin produced by the bacteria *Clostridium botulinum*. It is the most acute toxic substance known, and can lead to botulism, a serious and life-threatening illness in humans and animals causing acute paralytic attack on ingesting affected food. Justinus Kerner described BT as a "sausage poison" and "fatty poison," as the bacterium produced poisoning due to improperly prepared meat products.[1] It was Kerner, who first ascertained a possible therapeutic use of BT and coined the name botulism. In 1897, Emile van Ermengem discovered that a bacterium is a producer of the botulin toxin, which he named *C. botulinum*. In 1928, Tessmer Snipe and Hermann Sommer for the first time purified the toxin. In 1949, Arnold Burgen's group discovered, through an elegant experiment, that BT blocks neuromuscular transmission through decreased acetylcholine release.[1] Although chemically, botulinum is of seven different types, there are two forms of BT available commercially, Type A (Botox, Dysport and Xeomin), and Type B (MyoBloc) that are used for various cosmetic and medical procedures. The Food and Drug Administration (US) has only approved BT Type A for treatment of cervical dystonia (severe neck muscle spasm), severe primary axillary hyperhidrosis (excessive axillary sweating), blepharospasm (spasm of the eyelids) and temporary improvement in the appearance of moderate to severe glabellar lines (wrinkles). Type B BT has approval for cervical dystonia. More recently, BT has been suggested as part of the armamentarium for the management of various orofacial conditions, and a considerable body of literature has been developed describing or investigating its efficacy and safety.[2]

METHODS

Botox is available in a freeze-dried powder that clumps at the bottom of the vial. During reconstitution, the rubber seal on the vial should be wiped with an alcohol swab before injecting the desired volume of normal saline using a 5 mL, 25-guage needle syringe. Botox should be reconstituted after the journey. Agitation during transport may denature

the toxin and greatly reduces its duration of action. The entire solution may be given intramuscularly and not subcutaneously due to the presence of neuro-muscular junctions at the former site where the main mechanism of action of this toxin takes place. One mL insulin syringes can be used for injecting the solution as it gauges the dose accurately in minute quantities. A safe and reproducible injection point for BT around the converging area of the three muscles has been proposed and proved effective in clinical applications.[3]

Clinical Applications in Dentistry

The first-line treatment approach for temporomandibular disorders (TMDs) includes physiotherapy, exercises, behavioral type therapy, oral appliances, anti-inflammatory medications or some combination of these and rarely surgical intervention is indicated. BT can be a useful adjunct, particularly when these have failed to provide adequate relief, particularly in cases involving muscular hyperactivity. In treating temporomandibular joint (TMJ) dysfunction, the injection route may be either intraoral or transcutaneous, depending on the anatomic position of the targeted muscle. The superficial muscles, masseter and temporalis, may be palpated and injected externally according to anatomic landmarks.[4] Depending on the target muscle, dose of 10-50 U of Botox Type A per site with a total dose of 200 U in the masticatory system can be injected. Dose can be increased to 400 U maximum if other sites in the head and neck are included in the injection protocol. It may have a place as an adjunct to appropriate physical therapy in some cases of whiplash injury. Although there is a paucity of supportive research, there is a suggestion that BT may also have a supportive role in TMJ surgery.[4,5]

BT has useful treatment in refractory myofascial pain syndrome and have shown promise in various superficial neuropathic pain syndromes. Presumably BT work by breaking the spasm/pain cycle, giving the patient "window of opportunity" for traditional conservative measures to have a greater beneficial impact, but several studies suggest that a direct anti-nociceptive effect distinct from any reduction in muscle spasm may be at play. The major benefit of BT compared with standard therapies is duration of response. BT cannot be considered as "first line" treatment for any pain application; however, in refractory cases in which nothing else has helped, BT may offer the patient and physician a chance for improvement and perhaps even cure.[6-8] The dreaded "black triangle" usually tops the list of dentists' frustration after the preparation of crowns, bridges, and especially after implant and periodontal surgery. The patients are disappointed at the esthetic results because of the lost tissue. By injecting BT in these areas, it literally plump up papilla and is a minimally invasive way to create proper and more pleasing gingival contours. This is a very minimally invasive approach to a very difficult dental situation, and it completely satisfies the needs of the patient and gives the dental operator a very successful treatment outcome (Figure 1).

When an excess of gingiva superior to the maxillary anterior teeth is displayed upon full smile, it is termed a gingival smile. It is known by a variety of terms including – Gummy smile, high lip line and full denture smile.[9] This can be treated by targeting the levator labii superioris aleque nasi muscle. This muscle may be identified by asking the patient to move the tip of his nose. Injection of between 1 and 3 units of botoxat each superior medial naso-labial fold will relax this muscle. Without the elevation provided by this muscle, the upper lip will be lowered enough to cover the upper portion of the teeth, while the patient is smiling (Figure 2). Improvement of this area may be enhanced with a filler substance used adjunctively to diminish prominent superior naso-labial folds. The "downturned smile" can misrepresent emotions, imparting a sad or concerned appearance. This may be corrected with injecting BT into posterior aspect of the depressor angulioris muscle. This permits the zygomaticus muscle to act unopposed and elevate the corners of the mouth to a horizontal, more aesthetically pleasing position[10] (Figure 3). This muscle can be identified for injection by palpating along the jawline as the patient frowns or pulls down the corners of the mouth and the average dose of botoxis between 3 and 5 units per side.

BT has been shown to be effective in the management of sialorrhea. This involves the injection into the salivary glands, usually with electromyographicguidance.[10,11] Cases have been reported that intra-glandular injection of BT, into the submandibular glands, was helpful. Jongerius *et al.* reported that maximal salivary flow rate from the

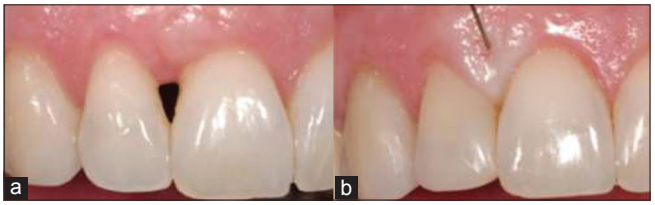

Figure 1: Black triangles corrected by botulinum toxin (a) Before (b) After

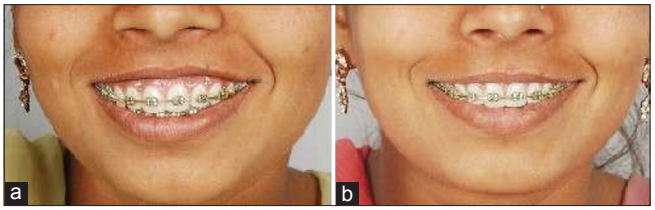

Figure 2: Correction of gummy smile after botox injection (a) Before (b) After

combined sublingual and submandibular glands was reduced by 51-63% in three of the four cases.[12] The clinical application of BT for the cosmetic purposes started after the effectiveness for treatment of blepharospasm. In 1989, the US Food and Drug Administration approved BT A for use in treating strabismus, blepharospasm, and hemifacial spasm in patients older than age 12 years. The first description of BT for the treatment of glabellar frown lines was in 1992. At that time, the use of this potent neurotoxin for cosmetic indications was an interesting footnote to treat strabismus, torticollis and other dystonias. Subsequently, physicians began to study and use the BT for a variety of cosmetic indications. Today, BT is the most commonly performed cosmetic procedure in the world.[13]

DISCUSSION

C. botulinum is a sporeforming, obligate anaerobe whose natural habitat is soil, from which it can be isolated without undue difficulty. The species *C. botulinum* consists of 4 genetically diverse groups that would not otherwise be designated as a single species except for their common characteristic of producing BT. BT exists in 7 distinct antigenic types that have been assigned the letters A through G. The toxin types are defined by their absence of the cross neutralization (e.g. anti-A antitoxin does not neutralize toxin Types B-G). In addition to

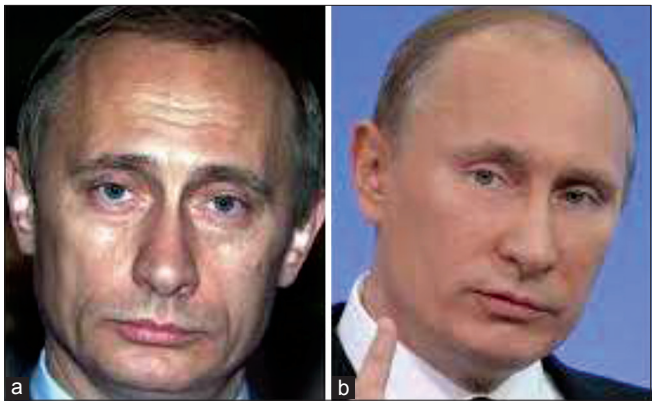

Figure 3: Correction of downturn smile by botulinum toxin (a) Before (b) After

C. botulinum, unique strains of *Clostridium baratii* and *Clostridium butyricum* have the capacity to produce BT. BT is a simple di-chain polypeptide that consists of a 100 kd "heavy" chain joined by a single disulfide bond to a 50 kd "light" chain. The toxin's light chain is a Zn++ - containing endopeptidase that blocks acetylcholine - containing vesicles from fusing with the terminal membrane of the motor neuron, resulting in flaccid muscle paralysis. The lethal dose of BT for humans is not known but can be estimated from primate studies. By extrapolation, the lethal amounts of crystalline Type A toxin for 70 kg human would be approximately 0.09-0.15 μg intravenously or intramuscularly, 0.70-0.90 μg by inhalation, and 70 μg orally.[14]

The toxin acts by preventing the release of acetylcholine from pre-synaptic vesicles at the neuromuscular junction resulting in the inhibition of muscular contraction. This blockade is temporary, varying from 3 to 4 months, after which sprouting of new axon terminals result in a return of neuromuscular function. Therefore, treatment with BT cannot be considered curative, but a palliative and symptomatic approach to the management of the problem. The toxin has also shown to block acetylcholine release at parasympathetic nerve terminals.[15] BTs work at the neuro-muscular junction through a four-step process (Figure 4):

1. Binding: The toxin must dissociate from the complex and attach to the target site
2. Internalization: The free toxin is internalized into an acidic vesicle
3. Membrane translocation into the cytosol: The light chain is released into the cytosol
4. Enzymatic cleavage of target protein: The light chain disrupts the specific target fusion protein complex responsible for vesicular docking on the inner surface of the cellular membrane, preventing acetylcholine release.[16]

Botox is a lyophilized BT A synthesized in bacterial culture as a single long chain protein nicked by bacterial proteases to produce the free toxin. It is purified from the culture solution by a series of acid precipitations to a crystalline

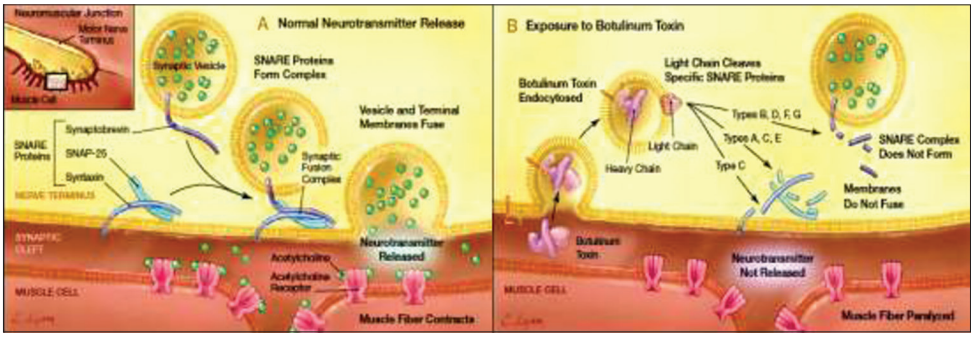

Figure 4: Botulinum toxin work at the neuro-muscular junction by blocking acetylcholine release at parasympathetic nerve terminals

complex consisting of the active protein and an associated hemagglutinin protein. The complex is re-dissolved in a solution of saline and albumin and sterile filtered (0.2 l) before vacuum drying. 100 U of BT A in a complex of 900 kd with 0.5 mg of human albumin and 0.9 mg of sodium chloride. The 100 U vial represents approximately 1ng of actual neurotoxin protein. It is recommended that BT A be stored in a freezer (5°C). It must be reconstituted with saline before injection. Myobloc (BT B) is produced by fermentation of *C. botulinum* Type B (bean strain) as a non-covalently associated neurotoxin complex with hemagglutinin and non-hemagglutinin proteins. After the fermentation process, the neurotoxin complex is purified through a series of precipitation and chromatography steps. Myobloc is marketed as a clear to light yellow solution in 3.5 mL glass vials with 2500, 5000, or 10,000 U of BT B (always at a concentration of 5000 U/mL) in 0.05% human serum albumin, 0.01 M sodium succinate, and 0.1 M sodium chloride at a pH of approximately 5.6. A 5000 U vial has approximately 10 ng of toxin protein.[16]

BT is the most poisonous substance known. A single gram of crystalline toxin, evenly dispersed and inhaled, would kill more than 1 million people, although technical factors would make such dissemination difficult.[14] BT A injections are well tolerated by most, an occasional patient finds these injections both painful and anxiety provoking. Various techniques have been described to reduce injection discomfort including topical refrigerants, nerve blocks and topical anesthetic creams. Although these modalities may be effective, they have a variety of disadvantages among them, including cost, time to onset, skin irritation and allergic skin reactions.[17]

CONCLUSION

BT has certainly been demonstrated to have significant value in the management of some types of orofacial pain, particularly myogenous TMDs in cases where the patient is unresponsive to the less invasive therapeutic modalities or, at times, in conjunction with them. Similarly, it has been proven effective in cases of severe sialorrhea. Cosmetic applications of the toxin have been well demonstrated in some areas such as correction of a gummy smile and black triangle. Although the drug is considered generally safe, there are a number of uncommon, relatively mild adverse reactions, but more recently, some severe, potentially life threatening side effects, distant from the site of injection have been described. Therefore, patients should be properly informed prior to consenting. The practitioner must ensure that the treatment is within his or her scope of practice and that he or she has the appropriate training, not only to administer the drug, but to deal with potential adverse effects.[3]

Hence BT can be certainly considered as a palliative prick.

REFERENCES

1. Patel DP, Thakkar SA, Suthar JR. Botulinum toxin: An aid for the neuromuscular correction of gummy smile – Review. Indian J Basic Appl Med Res 2013;2:764-72.
2. Bhogal PS, Hutton A, Monaghan A. A review of the current uses of Botox for dentally-related procedures. Dent Update 2006;33:165-8.
3. Colhado OC, Boeing M, Ortega LB. Botulinum toxin in pain treatment. Rev Bras Anestesiol 2009;59:366-381.
4. Ihde SK, Konstantinovic VS. The therapeutic use of botulinum toxin in cervical and maxillofacial conditions: An evidence-based review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;104:e1-11.
5. Sycha T, Kranz G, Auff E, Schnider P. Botulinum toxin in the treatment of rare head and neck pain syndromes: A systematic review of the literature. J Neurol 2004;251 Suppl 1:I19-30.
6. Racz GB. Botulinum toxin as a new approach for refractory pain syndromes. Pain Dig 1998;8:353-6.
7. Porta M, Perretti A, Gamba M, Luccarelli G, Fornari M. The rationale and results of treating muscle spasm and myofascial syndromes with botulinum toxin type A. Pain Dig 1998;8:346-52.
8. Abrams BM. Tutorial 36: Myofascial pain syndrome and fibromyalgia. Pain Dig 1998;8:264-72.
9. Patel DP, Thakkar SA, Suthar JR. Adjunctive treatment of gummy smile using botulinum toxin type-A (case report). J Dent Med Sci 2012;3:22-9.
10. Benson J, Daugherty KK. Botulinum toxin A in the treatment of sialorrhea. Ann Pharmacother 2007;41:79-85.
11. Wilken B, Aslami B, Backes H. Successful treatment of drooling in children with neurological disorders with botulinum toxin A or B. Neuropediatrics 2008;39:200-4.
12. Jongerius PH, Rotteveel JJ, van den Hoogen F, Joosten F, van Hulst K, Gabreëls FJ Botulinum toxin A: A new option for treatment of drooling in children with cerebral palsy. Presentation of a case series. Eur J Pediatr 2001;160:509-12.
13. Beer K, Cohen JL, Carruthers A. Cosmetic uses of botulinum toxin A. Cambridge, United Kingdom: Cambridge University Press; 2007.
14. Arnon SS, Schechter R, Inglesby TV, Henderson DA, Bartlett JG, Ascher MS, *et al.* Botulinum toxin as a biological weapon: Medical and public health management. JAMA 2001;285:1059-70.
15. Malcmacher L. Botulinum toxin for frontline TMJ syndrome and dental therapeutic treatment. Available from: http://www.dentaleconomics.Com. [Last accessed 2014 Aug 26].
16. Royal MA. Botulinum toxins in pain management. Phys Med Rehabil Clin N Am 2003;14:805-20.
17. Engel SJ, Afifi AM, Zins JE. Botulinum toxin injection pain relief using a topical anesthetic skin refrigerant. J Plast Reconstr Aesthet Surg 2010;63:1443-6.

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