Botulinum Toxin: Biochemical Aspects, Applications And Adverse Effects

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ABSTRACT
Botulinum toxin is one of the most potent bacterial toxins known and its effectiveness in the treatment of some pain syndromes is well documented. However, the efficacy of some of its indications is still in the process of being confirmed. Botulinum toxin, a neurotoxin with high affinity for cholinergic synapses, blocks the release of acetylcholine by nerve endings without interfering with neuronal conduction of electrical signals or synthesis and storage of acetylcholine. It has been proven that botulinum toxin can selectively weaken painful muscles, interrupting the spasm-pain cycle. In cosmetics, a small dose of botulinum toxin, can be used to prevent formation of wrinkles by paralyzing facial muscles. Botulinum toxin has been categorized into seven types, of which type-A preparations are currently the most widely used. In addition to the clinical and cosmetic uses of botulinum toxin, a number of adverse reactions have also been reported, therefore, it should be used with caution.

Keywords: Clostridium botulinum, botulinum toxin, clinical and cosmetic applications, Botox.

INTRODUCTION
Botulinum toxin is one of the deadliest toxins ever known to mankind. It is a neurotoxin (exotoxin) which is released by gram positive anaerobic sporing bacilli, Clostridium botulinum. In spite of its toxic nature, the clinical research has established the therapeutic benefits from this devastating substance. Various types of botulinum toxins (e.g. type A, B, C, D, E, F) have been clinically studied and their formulations are available in market such as Botox, which is the most commonly used preparation of botulinum toxin (type A). This review highlights some basic information to the readers related to its discovery, biochemical aspects, mechanism of action, clinical and cosmetic applications as well as on the adverse effects encountered after its use.

Historical Background
In early nineteenth century botulinum toxin was initially described as a "sausage or fatty poison" by a German physician Kerner (1786–1862) as this bacterium often caused poisoning by growing in improperly handled or prepared meat products (In latin botulus means sausage)¹,². It was also Kerner who first conceived a possible therapeutic use of botulinum toxin and suggested that the toxin can be used in small doses to block nerve function in various diseases¹,². In 1897, Emile-Pierre van Ermengem identified the bacterium Clostridium botulinum to be the causative agent of botulism while Snipe and Sommer in 1928 purified the toxin for the first time². In 1949, Burgen's group discovered that botulinum toxin blocks neuromuscular transmission and in the late 1960s, Scott and Schantz were the first to work on a standardized botulinum toxin preparation for therapeutic purposes²,³. Other bacteria that produce botulinum toxin are C. butyricum, C. baratii and C. argentinense⁴. Alan Scott, a San Francisco ophthalmologist, first applied tiny doses of the toxin in a medicinal sense to treat "crossed eyes" (strabismus) and "uncontrollable blinking" (blepharospasm)⁵.

In 1989, the first botulinum toxin preparation, Botox, was approved by the U.S. Food and Drug Administration (FDA) for the treatment of strabismus, blepharospasm, and hemifacial spasm in patients over
12 years of age⁷. Bushara and Parks for the first time showed that botulinum toxin injections inhibit sweating while treating patients with hemifacial spasm at Southend Hospital in England in 1993. They further showed the efficacy of botulinum toxin in treating hyperhidrosis (excessive sweating)⁸. In 2002, the FDA announced the approval of botulinum toxin type A (BTX-A) to temporarily improve the appearance of moderate-to-severe frown lines between the eyebrows (glabellar lines)⁹. BTX-A was later approved for the treatment of excessive underarm sweating. The acceptance of BTX-A use for the treatment of spasticity and muscle pain disorders is still growing with approvals pending in many European countries and studies on headaches (including migraine), prostatic symptoms, asthma, obesity and many other possible indications are ongoing. In 2009, its use for treating spasticity led a UK physician to successfully treat an Australian man who had been confined to wheelchair following a stroke 20 years ago¹⁰.

**Biochemical Aspects**

*C. botulinum* strains are divided into four different groups (groups I, II, III, and IV) based on their physiological characteristics¹¹-¹⁴. The toxins produced by these strains are categorized in seven antigenically distinguishable exotoxins such as A, B, C (C₁, C₂), D, E, F and G. Type A is the most potent toxin followed by the types B and F. Types A, B, E and rarely F are associated with systemic botulism in humans while types C and D cause toxicity only in animals¹³-¹⁵. All botulinum neurotoxins are produced as relatively inactive, single polypeptide chains with a molecular mass of about 150 kDa with a high degree of amino acid sequence. The polypeptide chain consists of a heavy (H) chain and a light (L) chain of roughly 100 and 50 kDa respectively, linked by a disulphide bond¹⁵-¹⁸.

**Formulations of Botulinum Toxin**

Botulinum toxin Type A formulations are currently the most widely used preparations but the other types are also emerging as clinically useful products¹⁵. Type B formulations are also available in the market. Different manufacturers produce specific products, which are not directly interchangeable and should not be considered as generically equivalent formulations as all these brands vary in their efficacy, units and cost. Each formulation of botulinum toxin is unique with distinct dosing, efficacy and safety profiles¹⁵,¹⁹-²². The preparations of botulinum toxin type A commercially available includes Botox®, Dysport®, Xeomin®, etc. where as type B includes Neurobloc® and Myobloc®.

**How Botulinum Toxin Works**

Botulinum toxin acts at four different sites in the body⁶,¹⁵,²³:
1. Neuromuscular junction,
2. Autonomic ganglia,
3. Postganglionic parasympathetic nerve endings and
4. Postganglionic sympathetic nerve endings that release acetylcholine.

The heavy chain of the toxin binds selectively and irreversibly to high affinity receptors at the presynaptic surface of the cholinergic neurons. This toxin-receptor complex is then taken up into the cells by endocytosis. The light (L) chain interacts with different proteins in the nerve terminal to prevent fusion of acetylcholine vesicles with the cell membrane. The disulphide bonds between the two chains are cleaved and the toxin is taken up into the cytoplasm⁶,²³-²⁶.

**Clinical Applications**

Botulinum toxins have found a wide variety of clinical uses in recent years in conditions like strabismus, symptomatic treatment of blepharospasm, hemifacial spasm, adductor spasmodic dysphonia, bruxism, teeth grinding, mandibular, cervical and focal dystonias along with various spastic movement disorders, hypercontractility of the internal anal sphincter, detrusor dyssynergy, vocal tremors and stuttering. Apart from so many medical uses, these toxins may also play an important role in management of headaches, migraine, hypersalivation, hyperhidrosis,
chronic lumbar pain, myofascial pain and some chronic conditions that hardly respond to any medical treatment. The uses of these toxins to avoid surgical procedures in case of spincterotomy in patients with chronic anal fissures and achalasia have shown greater achievement. Similarly some autonomic disorders resulting in hypersecretion of glands like hyperlacrimation, ptalism or gustatory sweating and intrinsic or allergic rhinitis have also reported to respond well to botulinum toxin\textsuperscript{2-7,15-35}. The uses of botulinum toxin in genitourinary disorders, ophthalmology, dentistry and variety of movement disorders have also been reported by some other workers\textsuperscript{36-40}.

**Cosmetic Applications**

The use of botulinum toxin for cosmetic purposes has become highly popular for the treatment of lines between eyebrows (glabellar), on the bridge of the nose and squint lines or crows feet at the corners of the eyes\textsuperscript{41,42}. Forehead horizontal and periorbital lines, nasolabial folds around the mouth, the thick platysmal bands around the neck, also known as “turkey neck” may also be efficiently treated by using the toxin\textsuperscript{43-45}. Along with the correction of muscles of upper one-third portion of the face, its use has also been noted for correction of lines, creases and wrinkles all over chin, neck, chest and smooth outlines of the jaws and cheeks\textsuperscript{41-47}.

**Adverse Effects**

The adverse effects associated with the use of botulinum toxin injection depends upon a number of different factors such as patient condition, frequency of injection, dose of toxin, route of administration and hypersensitivity reactions. Usually these adverse effects are mild and temporary in nature. They are mostly related to injection technique such as local redness and edema, transient numbness, mild nausea, bruising, swelling and mild pain. It is also observed that patients requiring high doses of toxin for severe wrinkles, altered facial anatomy or with pre-existing neuromuscular disease are at more risk for complications. Other complications include eyelid ptosis, focal facial weakness, headache, dysphagia, flu-like symptoms and hypersensitivity reactions. Some cardiovascular events such as arrhythmias are also reported after cosmetic use of botox injection along with inappropriate facial expression like drooping eyelid, double vision, uneven smile and loss of ability to close eyes. Sometimes unwanted weakness or paralysis may be caused to nearby muscles due to action of toxin which lasts for few weeks depending upon variation in patient condition\textsuperscript{7,15,48-54}.

**CONCLUSION**

The uses of botulinum toxins have gained high level recognition and acceptability by physicians and patients in recent years. It has been successfully used for the treatment of various ophthalmic spastic disorders, facial dystonias and cosmetological problems including wrinkles all over face and neck. However, it is strongly suggested that one should have a deep understanding of the exact mechanism of action of toxin, its potential in reducing chronic pain and weakness, functional anatomy of mimetic muscles as well as skills of procedure to achieve maximum benefits after the use of toxin preparations.

**REFERENCES**

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