

Beginner's guide to botulinum toxin: a general review

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Abstract

Introduction: Botulinum toxin is the poisonous neurotoxin produced by the bacteria *Clostridium botulinum*. Scientists have developed methods to use it for the betterment of mankind, utilizing its neurotoxic effects for the treatment of various disorders. Many diseases do not have complete or permanent treatment, in such cases the toxin can be used through "chemo denervation"⁽¹⁰⁾ method to give temporary relief to the patient.

Objective: The aim of the study is to review the general information of the botulinum toxin- its mechanism of action, uses, contraindication, effects etc.

Study design: An extensive literature search was carried on and the articles were thoroughly studied.

Results: Research and previous studies have shown that the neurotoxin gives positive results for the treatment of various disorders in both medical and dental field.

Conclusion: Botulinum toxin indeed provides a justifiable alternative to other more invasive procedures and thus clinicians including dentists should encourage its use for treatment of various disorders. Further research will also be necessary for gaining more knowledge about the neurotoxin and its effects.

Introduction

The gram negative bacterium *Botulinum clostridium* produces the deadly poison Botulinum neurotoxin. This toxin is responsible for causing "bilateral symmetric descending neuroparalytic disease"⁽¹⁾ by causing acetylcholine blockade which manifests as Botulism. In spite of the deadly effects of the toxin, in low doses, it is able to produce incredible therapeutic and cosmetic effects. There are 8 serological types of the toxin A, B, C1, C2, D, E, F, G of which toxins A is the most widely used.⁽²⁾

Botulinum Toxin A or Botox (Allerga, Inc, Irvine, Calif) as it is commonly known, is a name that many of us think to be related to a cosmetic. On contrary to this belief, Botox was first approved by the FDA in 1989 for its therapeutic purpose for the treatment of Strabismus and blepharospasms.⁽³⁻⁵⁾ Botulinum toxin B though less popular has been approved by FDA for the treatment of cervical dystonia while Subtype F is under research for its use in patients resistant to A and B.⁽⁶⁾

Botulinum toxin A is used for the treatment of a variety of disorders. Mostly it is used for the treatment of strabismus, blepharospasm, cervical dystonia, gustatory sweating syndrome, relief from pain and muscle hyperactivity, overactive bladder, anal fissures etc.⁽⁷⁻⁸⁾ Researchers and clinicians have reported that it is also used for the treatment of sialorrhea, Frey's syndrome, chronic facial pain, hemifacial spasms etc in the orofacial region.⁽⁹⁾

The ability of the toxin to cause muscle paralysis is the main reason for its extensive popularity in controlling muscle hyperactivity and spasm. Thus Botulinum toxin A therapy should be encouraged as it is minimally invasive and can replace complex surgical procedures and also due to many other benefits that we will learn about further in the article.

History

In 1949 Burgen was first to discover that Botulinum toxin was able to block neuromuscular transmission.⁽¹⁾ In 1989 Botulinum toxin A was approved by the FDA under the trade name BOTOX for the treatment of blepharospasms, strabismus and hemifacial spasms for patients under 12 years of age.⁽¹⁰⁾ In 2000 FDA approved it for the treatment of cervical dystonia,⁽¹⁾ in 2002 for the treatment of frown lines, in 2004 for the treatment of axillary hyperhidrosis,^(11,12) in 2010 for the treatment of upper limb spasticity, in 2013 for the treatment of overactive bladder and in 2016 approved for the treatment of lower limb spasticity.

Mechanism of Action

The toxin acts by inhibiting the acetylcholine release at the neuro muscular junction thus causing muscle paralysis. It acts in the following steps-

1. Toxin binds to the nerve membrane.
2. It goes into the nerve.
3. The toxin is cleaved by the proteolytic enzymes of the neuron.
4. The products of the reaction interfere with vesicle fusion to plasma membrane.
5. Exocytosis of acetylcholine is inhibited.
6. Neuromuscular blockade occurs.⁽¹³⁾

Recovery phase:⁽²⁾ nerve growth factor⁽¹⁴⁾ 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.

Composition

Each Botox vial consists of:⁽¹⁵⁾

- 100 units (U) of Botulinum toxin type A
- .5milligram of Human Albumin
- .9milligram of Sodium Chloride

These ingredients are packed in a sterile dry form without any preservatives. Shelf life is 21 months when kept refrigerated.

1 unit of botulinum toxin A is the amount of toxin that can kill 50% (LD 50) of a group of 18 – 20g Swiss Webster Mice when injected intraperitoneally. In human LD 50 is 40units/kg that is approximately 2800units for a 70kg adult.⁽²⁾

Preparation

1-5 ml of saline is gently injected onto the sides of the walls of the vial. Care should be taken as the solution denatures due to mild bubbling or agitation. The pH of the solution is 4.2 to 6.8. ⁽¹⁾ This solution can be used within 4 hours if kept at 2-8 degree Celsius (C). While injecting the following steps may be followed for better results: ⁽¹⁶⁾

1. First a hypersensitivity test is performed to check if the patient is allergic to the solution.
2. Pre injection and post injection pictures are taken to compare the effects.
3. Makeup and dirt is removed from the face or any other part of the skin.
4. The site of injection is disinfected using isopropyl alcohol.
5. 10ml tuberculin syringe (calibrated) with a needle of 26-30 gauge is used.⁽¹⁷⁾
6. Practitioners use 2 types of injection techniques A. Single point B. Skewered method.
7. While injecting, the muscle is pinched gently to reduce the pain.
8. The needle is inserted parallel to the plane of the muscle.
9. The solution is deposited while withdrawing the needle.
10. Injections should be 1-2 cm apart from each other.
11. The area is not massaged as this will cause the solution to diffuse into unwanted areas.
12. Pressure is applied in the injection site with cotton to prevent bleeding.
13. To reduce pain, ice or topical anesthesia is applied.

Uses of Botulinum Toxin A

According to the mechanism of action, Botulinum toxin A has been tested for the treatment of different conditions and has been found to be effective in many cases. Apart from the FDA approved uses, botulinum toxin A is also used as an off label drug for the treatment of many conditions. The uses of this toxin can be classified as dermatological uses and non dermatological uses.

1. **Dermatological Uses/ Cosmetic Uses:** FDA has approved Botulinum toxin A for the treatment of Axillary hyperhidrosis, Glabellar lines. Other than these, the off label uses are for the treatment of

Sweating disorders (eg. Hailey-Hailey,⁽¹⁸⁾ Granulosis rubra nasi, Pitted keratolysis, Dyshidrotic hand eczema, Chromhidrosis, Inverse Psoriasis,⁽¹⁹⁾ Eccrine hydrocystomas, Eccrine Angiomatous Hamartoma, Aquagenic syringal acrokeratoderma) and for the treatment of Pain and itching disorders (eg. Notalgia Paresthetica, Brachioradial pruritus, Vulvodinia, Raynaud Syndrome, Lichen simplex chronicus,⁽²⁰⁾ Post-herpetic Neuralgia, Leiomyoma-related pain, Thelalgia).⁽²¹⁾

2. **Non Dermatological Uses:** Ophthalmological disorders for example- Reduced lid retraction, Blepharospasm, Apraxia of lid opening, Nerve palsies, Lacrimal hypersecretion, Pain relief in acute angle closure glaucoma, Congenital nystagmus, Exposure keratopathy. Gastrointestinal disorders for example- Achalasia, Anal fissure, Biliary dyskinesia. Neurological disorders for example- Hemifacial spasm, Facial asymmetry, Oromandibular dystonia, Cervical dystonia, Spasmodic torticollis, Headache, Synkinesia, Gustatory sweating, Migrain headache.

Urological and Gynaecological disorders for example- Bladder overactivity, bladder syndrome, Detrusor overactivity, Detrusor sphincter dyssnergia, Pelvic pain, Outflow obstruction symptoms, Urinary retention.

Presently Botulinum toxin is extensively used in the field of dentistry for the treatment of- Gummy smile, Black triangle of the gums, implant and surgery (to reduce the overloading on masticatory muscles), Bruxism, Pathological clenching, Trigeminal Neuralgia, An adjunct to orthodontic treatment, myofascial pain, Temporomandibular disorders etc.

Contraindications

The absolute contraindications are: ⁽²²⁾

- Hypersensitivity to the toxin.
- Immunocompromised patients.
- Infection at injection site

The relative contraindications are: ⁽¹⁶⁾

- Pregnancy
- Lactation
- Eaton Lambert Disease
- Myasthenia Gravis
- Motor neuron diseases
- Psychological disorders.
- Patients on medication that interacts with neuromuscular transmission Eg. Aminoglycoside, penicillamine, quinine etc.⁽²³⁾

Complications and Adverse Effects

There are not many severe side effects reported due to the use of botox. Local effects are mostly temporary for example –

Soreness of muscle while injecting, weakening of injected muscle, bruising. These can be managed by using analgesics like NSAIDS, icepacks. Other more serious side effects that have been reported by researchers are.⁽¹⁾

Ptois- managed by using Phenylephrine apraclonidine eyedrops.

Asymmetry of face – Managed by using proper technique and constant doses.

Headache Antibody development Necrotizing fasciitis.

Limitations

- Masticatory function are limited after the use of Botox, this effect will last until the effect of the drug remains after which normal function will return.⁽¹⁶⁾
- Botox treatment is short term (approx 6 months) reinjection is needed after the effects wears off.
- Reinjection should only be done when the previous effects have completely disappeared. Premature injection causes increase in antibody against botox.
- Injection at wrong site gives asymmetric results.
- A vial of botox has a very high cost.

Conclusion

Botox is undoubtedly an important and effective treatment option for many disorders. Further research and studies are necessary for better understanding of the compounds and its effects. Application of botox is minimally invasive and patient compliant having the least adverse effects. Its use should benefit both the clinician by decreasing chair side treatment time and the patient as the treatment is less painful and convenient.

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