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Review Article

Botox- the wonder poisonous healer

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ABSTRACT

Botulinum toxin A has a wide variety of medical applications, which are related to the blockade of acetylcholine and often are associated with abnormal muscle contractures. The use of botulinum toxins has also revolutionised the treatment of various dental conditions like bruxism, gummy smiles, Frey's syndrome spastic disorders, hypersalivation, orthodontic relapse, facial dystonias and temporomandibular disorders. The list of possible new indications is rapidly expanding. Many of these conditions are discussed with regard to their treatment with Botox compared to conventional treatments.

1. Introduction

The demand for cosmetic services has increased considerably worldwide. A lot of medical specialties administering cosmetic services have seen a rise in therapies that enhance the physical appearance, reverse the effects of aging, and improve esthetics.[1] Certain clinical scenarios require surgical intervention whereas majority of other situations require a conservative, quick, easy and relatively inexpensive non surgical approach.[2]

Frequent uses of Botulism neurotoxin for smoothing of the glabellar lines, crow's feet, bunny lines, upper and lower circumoral lip lines, marionette lines, dimpled chin and vertical neck lines have placed it relatively higher on demand list than an other esthetic treatment. Along with the uses in cosmetology Botox has been used in curing conditions like hyperhidrosis, strabismus and blepharospasm. Of late its significance has increased in dentistry for the treatment of oral conditions like excessive gingival display, temporomandibular disorders, bruxism etc.[3]

2. History

In the 19^{th} century the Kerner J. initially introduced the thought of a plausible therapeutic application of botulinum toxin, which was referred to as "sausage poison".[4]

In the late 1800s, Muller first used the term botulism which is derived from the Latin word botulus (meaning sausage). In 2002, United States Food and Drug Administration approved the use of Botulism neurotoxin for transient elimination of frown lines between the eyebrows (glabellar lines). From then on, it has been widely accepted as a cosmetic and therapeutic agent.

2.1. Mechanism of action

Botulinum toxin is a neurotoxin obtained from Clostridium botulinum. The bacteria contain eight antigenically differing exotoxins (A, B, C_1, C_2, D, E, F and G).[5]

It binds on the presynaptic sites at the cholinergic nerve endings and reduces the discharge of neurotransmitter, causing a neuromuscular blocking action. This partially

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paralyses the muscle for three to four months. This action built the foundation for its use therapeutically. Recovery occurs through development of a new neuromuscular junction.[6]

2.2. Contents of the vial

The two types of vials available in India are 100 and 50 unit vials.

Each 100ML vial of botulism neurotoxin has:

1. 100 Units of botox type A,
2. Milligrams of Human albumin,
3. And 0.9 milligrams of sodium chloride in a sterile, vacuum dried conformation unaccompanied by any preservative.[7]

2.3. Potency

Its potency is communicated in the form of mouse units, with 1 mouse unit equal to the median lethal dose (LD_{50}) for mice. One unit of botox is consistent with the calculated median peritoneal lethal dose (LD_{50}) in 18- 22 grams of female Swiss- Webster mice. There are two preparations of botulinum neurotoxin A: Dysport and Botox. Botox vials contain 100 U, whereas Dysport vials contain 500 U. The potency of Botox units in comparison with Dysport units is about 1:4.

The life threatening dosage of Botulism neurotoxin is calculated to be around 3,000 U. The maximum permissible dosage in a session is approximately 80- 100. This signifies that 30 vials will have to be injected before any possibly lethal outcome is obtained. There is a great disparity in the therapeutic dose and the lethal dose that a life threatening overdose is almost impractical.[2] Adequate pH of the solution is approximately 4.2 to 6.8.[8]

2.4. Reconstitution and storage

Serotype A is the sole commercially obtainable form of the neurotoxin for clinical use.[9]

Botox is stored straight away on receiving it in the freezer at -5°C or lower. The recommended reconstitution is with sterile saline unaccompanied by any preservative; it is diluted with 0.9% sodium chloride. Certain researchers advocate that reconstituting it with saline along with added preservatives (0.9% benzyl alcohol) decreases bacterial growth and results in decrease of local anesthetic effect. It may also increase the shelf life and potency. It should be reconstituted right before administration for maximum effects.

The neurotoxin is denatured easily on bubbling or shaking; the diluent is carefully injected on the inner wall of the vial and the vial is discarded if vacuum is not ble to draw the diluent inside. Final dilution of the neurotoxin is kept according to clinician proclivity; 100 units generally are mixed with 1-10 ml of diluent.

After reconstitution, the neurotoxin is kept in the refrigerator at 2-8°C. It is now to be used in under four hours.[5]

2.5. Technique of injection

Prior researches recommended 10 to 20 units or more at each site to show results in the desired muscles of facial expression. However, appropriate results using even 2.5 units at each site can be achieved.

Males need a minutely higher dosage at each site (up to 5 units on each site), other-wise it results in only mild to moderate refinement of hyperfunctional rhytids, with shorter duration of action. Diluted neurotoxin is pulled up into 1.0 ml syringes using an 18- gauge needle to reduce agitation.[9]

Preoperatively, makeup should be removed from the patient's face.[8]

Patients are advised against taking aspirin and other drugs temporarily which affect bleeding time prior to administration of the neurotoxin. This results in reduction or elimination of facial bruising that may be present for a few weeks to months. In case of minimum or no bruises after administration of botulism toxin, the patient can get back to work in under an hour.

Botox is injected with a 30 gauge needle. The application of local anaestheic is unessential. Application of alcohol can be done at the injection sites but it must be dried prior to injecting botox.[9]

Electromyography (EMG) is a useful tool before injections to precisely identify muscles beneath the wrinkles. It is tedious and costly; hence, it is not frequently practiced clinically.

These injections are given through a single-point or a skewered method. The syringe is pushed parallel to the muscle fibers. The plunger is pushed while the needle is slowly removed simultaneously. Administration of the toxin should be done at sites around 1 to 2 cm apart and it should not be injected in areas where paralysis is not desired. Carefully pinching the muscle at the time of injection helps reduce discomfort and ensures superficial administration of the toxin. Cold packs reduce pain at the time of Botox administration. Rubbing after injecting botox is not advised to avert its dispersion into surrounding musculature. Extreme exertion must be circumvented for 24 hours post therapy. Often 2 or 3 appointments are necessary before the patient is complacent with the results.[8]

Skin markings and sites of injections are made over the probable belly of the muscle and not in the region of maximum skin depression, which can be somewhat at a distance from the effector muscle. For much wider, deeper muscles like the corrugator supercilii, it is more effective to administer the toxin deeper to the muscles (frontalis and orbicularis) or directly into the maximum thickness of

the muscle. Usually, four or five administration areas at a dosage of 2.5 to 5.0 units each area are adequate in reducing local muscular tonicity and voluntary contraction of the corrugators. The desired effects may not be reached on more superficail applications.[9]

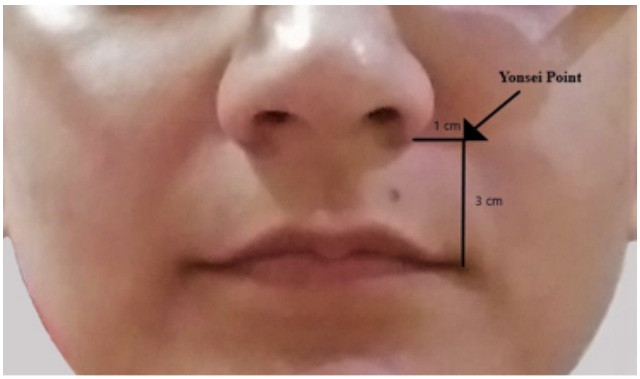
2.6. Dental applications of botox

2.7. Gummy smile

Over-contraction of the upper lip muscles is frequently the cause of excessive gum exposure. The muscle that plays a major role in this is the levator labii superioris alaeque nasi. A number of surgical procedures have been cited in numerous researches for correcting overactive upper lip but they are not generally used for the treatment of gummy smile.

Botox can be injected in small doses to reduce the exposure of gingiva when smiling.[3]

Polo M. recommended administration of the neurotoxin at levator labii superioris, levator labii superioris alaeque nasi, levator labii superioris/ zygomaticus minor overlap and in extreme cases at depressor nasii and orbicularis oris also. The optimal dosage is 2.5 U at each side in the levator labii superioris & levator labii superioris alaeque nasi, 2.5 U at each side in the levator labii superioris/zygomaticus minor sites, and 1.25 U at each side in the orbicularis oris muscle. Recently Hwang and colleagues from the Yonsei University College of Dentistry, Korea have put forward the injection site for botox A, and termed it YONSEI POINT and they have proposed a dosage of 3U at each Yonsei point. This point is found in the mid of the triangle formed by levatorlabiisuperioris, levatorlabiisuperiorisalaequenasi, and zygomaticus minor.[2]



2.8. FREY'S syndrome and sialorrhea

Certain autonomic diseases have been found to be responsive to Botox such as achalasia, hyperhidrosis and Frey syndrome.[10] It has also been highly efficacious and comparatively safe in the treatment of acute postparotidectomy salivary fistulas.[3]

Botox is given for treating sialorrhea. It is administered in the parotid and submaxillary salivary glands and impedes stimulation of cholinergic receptors. Fuster Torres MA reviewed salivary gland administration of botulinum toxin for treatment of sialorrhea. In the research different authors have advocated varying dosages of Botox ranging between 10-100U. A reduction in saliva production was found after botox administration, and the therapeutic effect lasted 1.5-6 months.[11]

2.9. Orthodontic relapse

The action of muscles play a principal role in the position of the dentition and post orthodontic therapy relapse has been a major problem because of them. Typically, relapse is caused by the overactive mentalis. Botox helps relax the muscle activity and over time the muscle can be trained to function normally.[11]

2.10. Bruxism

Botox has also been used in relieving the symptoms of bruxism. Initial reports on use of botox type A in bruxism was by Van Zandijcke and Marchau.. They reported the treatment of a brain damaged patient with severe bruxism using 100 U of BONT A administration into the temporalis and masseter muscles.[3]

BTX can be used in the treatment of several bruxism-related conditions like developmental disabilities, night time bruxism and myofascial pain. The neurotoxin reduces myofascial pain. Present day treatment with Botox includes bilateral administration in the masseter and temporalis muscles. But, the administration of Botox in the temporalis muscle has not definitively been found to eliminate bruxism. Rather, the bilateral action of Botox on the masseter muscles, slightly superior to the angle of the mandible, has been found to be successful in numerous research studies.

This toxin partially paralyzes the muscles and decreases the capacity to forcefully clench and grind the jaws hence striving to retain enough muscular tonicity to enable normal activities such as talking and eating.

The neurotoxin may impede periodontal mechanoreceptors giving a solution to troubles with mouth closing relating to bruxism. Bruxism can also lead to masseteric hypertrophy. Botox is a significantly less invasive option for this condition in comparison to surgery. It generally requires five to six administrations in the masseteric and termporalis regions, and less commonly in the lateral pterygoid muscles. Administration takes a few minutes for each side, onset of the effects occurs by 24 hours and lasts for about 12-15 weeks. Occasionally, adverse effects may occur, such as bruising, but this is quite rare.[11]

2.11. Dental implants

Excessive force of the muscles of mastication can result in high pressure and prevent osseointegration of implants and/or fracture callus formation. Relaxation of these muscles with botox injections result in an uneventful osseointegration.[3]

2.12. Complete denture patients

Patients who have been edentulous for a long period of time face the difficulty of getting used to a new set of dentures due to irregular and uncoordinated muscle activity which results from rapid change in vertical dimension associated with new prosthesis. Botox treatment can be helpful in such patients.

2.13. Fractures and surgery

The neurotoxin, in high quantity, can be used as a pharmaceutical splint. It decreases muscle contraction before resetting and during rehabilitation post fracture of a facial bone. Kayikvioglu et al. conducted a small research to scrutinize the use of botox type A as an additional line of treatment in zygomatic fracture fixation surgery, in order to reduce the number of fixation sites and to avert dislocation of the zygomatic bone. The interim paralysis of the masseter muscles after botox injections permitted for fewer miniplate and/or microplate insertions, and resulted in no complications related to either the botulinum toxin injections or surgical procedures. Similar benefits were also found in treating surgical reduction of mandibular and condylar bone fractures.[3]

2.14. Diagnostic AID

Muscular or pulpal pain can be differentiated with botox in patients having long term intermittent toothache. Botulinum toxin type A can be both prophylactic as well as diagnostic in case when pain from the anterior temporalis muscle is referred to the teeth.[3]

2.15. Masseteric hypertrophy

Masseter hypertrophy is a benign condition with varying etiology, like bruxism, temporomandibular disorders, malocclusion etc., but has ambiguous causative factors in the majority of cases.[2] In various studies, the administration of small quantities (e.g., 30 U per side) of the neurotoxin in masseter muscles resulted in a constant decrease in its hyperactivity. With time, in most people, decrease in masseter hyperactivity has been found to result in accompanied decrease in masseter size (maximum reduction 35.4%).[3] The possible complications of this approach are external scar and damage to the mandibular branch of facial nerve, change in bite pressure, speech disturbance, muscle tenderness, asymmetrical face, and prominent zygoma.[2]

2.16. Mandibular muscle spasm

Botulinum neurotoxin administration in the masticatory musculature diminishes the action of hyperfunctional or spastic muscles.[3]

2.17. Temporomandibular disorders

Many treatment methods are available to treat Temporomandibular disorders (pain medications, muscle relaxants, accupressure, accupuncture, intraoral appliance therapy, surgery). Comparing different treatment options. botox is a newer innovation for treating TMDs associated with the hyperfunctional musculature. The temporalis and masseter muscles are mostly affected and administered with the toxin. 10-25 U of toxin is administered in temporalis muscle, 25-50 U in the masseter muscle and 7.5-10 U in lateral pterygoids.[12] Botox notably decreases the strength, frequency and duration of recurrent pain if administered properly.

2.18. Facial nerve palsy

Facial nerve palsy usually appears with hyperlacrimation (crocodile tears) associated with salivation because of the connection between secretomotor fibers of salivary gland to lacrimal gland. Administration of the neurotoxin in the lacrimal gland has been a pertinent treatment option.[13]

2.19. Headache, migraine, trigeminal neuralgia

In trigeminal neuralgia, botox produces an anti inflammatory action by blocking an inflammatory neuropeptide calcitonin gene-related peptide (CGRP). It can also reduce pain is by decreasing the release of glutamate peripherally (glutamate is responsible for inflammation, pain and edema).

2.20. Plathero spasms and oromandibular dystonias

Oromandibular dystonia is a muscle dysfunction and pathology that involves the masticatory and lower facial muscles. It can cause unintentional opening and closing of the mouth in vertical, lateral and protrusive directions. Typically this also leads to involuntarily chewing of the soft tissues in the oral cavity and interferes with regular mastication and speech. Masseter injections of botox have been researched to fix some of these muscle dysfunctions. Pletharo spasms are excessive and involuntary closure of the eyelids which is frequently caused by spasms of the orbicularis oculi.[2]

2.21. Facial aesthetics

For lateral canthal rhytids (crow's feet), three or four injections are given avoiding pretarsal orbicularis of the upper and lower eyelid. This is achieved by directing needle insertion temporal to the lateral canthus near the lateral orbital rim and distant to the eyelid margin. The procerus muscle can be injected at one or two sites just beneath the transverse wrinkle at the nasal bridge. This superficial plane also avoids orbital injection. Hyperkinetic horizontal forehead furrows seem to respond favorably to either subcutaneous or intramuscular injection of the toxin, presumably since the frontalis is the only active muscle in this region. Partial paralysis, rather than complete denervation, may also be more suitable in some patients to avoid brow ptosis. These injections are most effective by administering a uniform grid whereby approximately nine or more sites are injected across the forehead. Three or more sites on each side are placed in a vertical line above the mid-eyebrow. Additional sites are placed vertically in the mid-forehead region. This results in frontalis muscle weakening at the medial aspects. A harmonious treatment of the forehead avoids focal areas of remaining function that can become quite noticeable in complete absence of adjacent furrows. Generally, 2.5 units (0.1 ml) are given at each site. Injections over the lateral eyebrow are abstained from to prevent the possibility lateral eyebrow ptosis. Cosmetics can be used directly after the injection.

The zygomaticus minor muscle originates close to the zygomaticus major muscle and inserts medially into the upper lip. Both of these muscles deepen the nasolabial fold. Utilizing lower dosage (2.5 units/ 0.2 ml) near the areas of origin, injecting it mostly at the edge of the lower part of the orbicularis of the lower eyelid, the clinician can soften their additional effect on the lateral canthal rhytids and nasolabial folds. One or two injections given on the mid to lateral malar eminence are generally sufficient to obtain the desired effect without complications, particularly paralysis of the same side of the upper lip.

The neurotoxin has also been shown to be pertinent in reducing fine perioral rhytids (lip stick lines) by being the treatment of choice. About 1.0 to 1.5 units of the neurotoxin is administered adjacent to the fine vertical rhytids over the orbicularis oris muscle close to the vermilion ridge. An additional striking effect is the appearance of thicker lips because the sphincter muscle is weakened along the vermilion border to gain a more everted position.[9]

2.22. Contraindications

Patients should be treated with exceptional prudence who are:

1. Mentally unstable or those that have dubious motives and impractical expectations.
2. Those relying on unimpaired facial expressions for a living.
3. Those that are plagued with a neuromuscular disorder.
4. Allergic to the ingredients of BTX-A or BTX-B.
5. Under medications that interferes with neuromuscular impulse transmission and bolsters the effects of Botox (e.g. aminoglycosides, penicillamine, quinine, and calcium blockers).
6. Pregnant or lactating (BTXs are classified as pregnancy category C drugs).[3]

2.23. Future research

BTX- A has increased its clinical span of uses, but the risk of developing antibodies limits the repeated use of high-dose injection. Other serotypes of botox are being researched on as useful options. Botox type F is different from type A, majorly by its decreased potency, efficacy and lesser duration of action and blocks another SNARE protein in comparison to type A toxin. Therefore, a combination of toxins A and F has been suggested to reduce the total units and overall antigenic dose.[5]

3. Conclusion

The application of botox in dental and allied fields has drastically transformed the therapy of numerous spastic disorders, facial dystonias and temporomandibular disorders. Harmful effects are generally mild and temporary.

4. Highlights

The most common substantive complication is unwanted weakness, and this reduces as the toxin disintegrates. Eyebrow ptosis, lid ptosis, neck weakness, dysphagia, and diplopia may exist. Knowledge of the muscle anatomy and experience help the clinicians avoid adverse effects. In future, the evolution of new efficacious toxins with increasing effectiveness and duration of action will aid this expanding and interesting field of chemodenervation.

5. Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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