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Antiaging Effect of Botox Exotoxin in Cosmetic Dermatology

Miss. Shrutika J. Thakur

(Student, K.T.Patil college of Pharmacy,Osmanabad)

Dr. Amol A. Joshi

(Principal at K.T.Patil college of Pharmacy,Osmanabad)

Mrs. Mohini S. Khandagale

(Assistant professor at K.T.Patil college of Pharmnacy,Osmanabad)

Abstract - Botulinum toxin (Botox) consists of 7 types of neurotoxins; Botox A is used for several disorders in the field of medicine, particularly in dermatology, for cosmetic purposes. It is produced by the bacterium *Clostridium botulinum* and can be used as a treatment to reduce the appearance of wrinkles in the upper areas of the face, elevate the eyebrows and treat problems such as hyperhidrosis, lichen simplex, pompholyx and acne vulgaris. Botulinum toxin injection for treatment of facial wrinkles is the most frequently performed cosmetic procedure in the United States, Treatment of frown lines and crow's feet, which are the cosmetic indications approved by the U.S. Food and Drug Administration, and horizontal forehead lines, offers predictable results, has few adverse effects, and is associated with high patient satisfaction. Botulinum toxin is a potent neurotoxin that inhibits release of acetylcholine at the neuromuscular junction. Botulinum toxin injection is contraindicated in persons with keloidal scarring, neuromuscular disorders (e.g., myasthenia gravis), allergies to constituents of botulinum toxin products, and body dysmorphic disorder. Minor bruising can occur with botulinum toxin injection.

KeyWords: *Clostridium botulinum,* hyperhidrosis, lichen simplex, acne vulgaris, pompholyx.

1. INTRODUCTION

Botox is used medically to treat certain muscular conditions, and cosmetically to remove wrinkles by temporarily paralyzing muscles. It is made from a neurotoxin called botulinum toxin that is produced by the bacterium *Clostridium botulinum*

Botulinum toxin is a neurotoxic protein produced by the bacterium *Clostridium botulinum* and related species. It prevents the release of the neurotransmitter acetylcholine from axon endings at the neuromuscular junction and thus causes flaccid paralysis. Infection with the bacterium causes the disease botulism. There are eight types of botulinum toxin, named type A–H. Types A and B are capable of causing disease in humans, and are also used commercially and medically. Types C–G are less common; types E and F can cause disease in humans, while the other types cause disease in other animals. Type H is considered the deadliest substance in the world – an injection of only 2 ng can cause death to an adult. Botulinum toxin types A and B are used in medicine to treat various muscle spasms and diseases characterized by overactive muscle. The Food and Drug Administration approved the use of botulinum toxin for glabellar wrinkles in 2002. Treatment of other areas like forehead, crow's feet, nasal wrinkles, chin, and platysmal bands are off-label uses. Applications in the treatment of facial asymmetry involving the upper, middle and lower face and neck have been suggested. Botulinum toxin is used to treat conditions such as hyperhidrosis, tension headaches, migraine headaches, cervical dystonia, torticollis, adductor and abductor laryngeal dystonia, lingual dystonia, limb dystonia, poststroke spasticity, back pain, and other conditions characterized by undesirable muscle contraction such as spastic conditions. Botulinum toxin has been approved for blepharospasm, axillary hyperhidrosis, strabismus, and cervical dystonia. The Food and Drug Administration approved the cosmetic use of botulinum toxin type A for glabellar wrinkles in 2002-12. The potential cosmetic uses of botulinum toxin that are suggested in current literature.

Upper face

1. Glabellar wrinkles
2. Upper nasalis wrinkles (bunny lines)
3. Lateral canthal wrinkles (crow's feet)
4. Horizontal forehead wrinkles
5. Asymmetric brows
6. Thyroid ophthalmopathy patients with pronounced glabellar wrinkles
7. Lower eyelid wrinkles

Midface

1. Lower nasalis wrinkles, nasal flare
2. Short upper lip, gum show
3. Perioral wrinkles (smokers' lines)
4. Facial asymmetry

Lower face

1. Mouth frown, melomental folds, drooping labial
2. commissure
3. Peau d'orange chin
4. Mental crease
5. Lower facial asymmetry

Neck

1. Horizontal necklace lines
2. Vertical platysmal folds

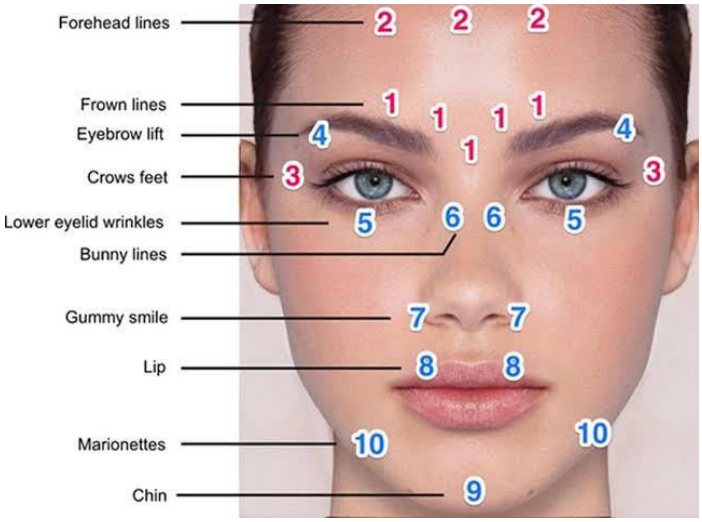

Fig -1: Facial parts

Aim: Antiaging Effects of Botox Exotoxin in cosmetic Dermatology.

Objective:

- To reduce fine lines and wrinkles by paralyzing the underlying muscles.
- To treat excessive sweating, migraines, muscular disorders, and some bladder and bowel disorders.
- To temporarily paralyze muscle. This reduces the appearance of facial wrinkles.

2. HISTORY AND TYPES OF BOTOX

BT is a powerful neurotoxin produced by bacterium *Clostridium botulinum*. First time in 1897, it was identified in Belgium by Professor Emile van Ermengem, following the investigation of fatal food poisoning caused by macerated ham consumption.[5] It was named after the disease botulism originally associated sausage meat (Latin-botulus for sausage). There are seven types of Botulinum toxin (A, B, C, D, E, F, and G). Flaccid paralysis of motor and autonomic nerves occur due to classic foodborne disease caused by BT serotypes of A, B, and G. Type B-BT discovered in 1910, and isolation of type A-BT begun in 1920.[5] During the second world war, the research continued at Chemical Warfare Laboratories of Fort Detrick, Maryland in the United Kingdom for biological warfare as a potent neurotoxin (agent ×). In 1989, Ipsen pharmaceuticals bought Porton chemicals and are the only commercially available forms of Botulinum toxin (Dysport)®.[5]

Dr. Allen Scott performed a first clinical test in 1978 using type-A BT.[5] His results were published in 1980 led to the extensive use of BT by ophthalmologists for the treatment of blepharospasm. With the advent of BT-A in 1990, effectively launched as nonsurgical esthetic medicine in this modern era.[6] In 1973, a small dosage (35–50 units) of BT-A has been shown to be safe and effective for hyperfunctional lines and facial rhytids. The median lethal dose is considered to be 2500–3000 units which are approximately 100th of the lethal dose. Therefore, BT-A has an extremely high therapeutic index.[7] It is commonly used as a part of overall facial rejuvenation. A myriad of application for BT-A has been explored

not only for aging but also for a long list of neuromuscular, glandular disorders, muscular countering, and various pain syndromes.[8]

Out of seven serotypes of BT, five are useful in human neuromuscular junction (BT-A, B, E, F, and G). Three types of BT are commercially available. Botox® and Dysport® (both BT type A) and Neuroblock® (BT type B). Allergan produces Dysport® by Ipsen pharmaceuticals and Neuroblock® by Elan, Ireland.[5]

Fig:2 Marketed formulation

Safety: Botox is a drug with a broad margin of safety (lethal dose 50% (LD50) in humans can reach up to 40 U/kg BW). Therefore, its use in cosmetics is relatively safe. Botox is relatively safe and effective for treating facial wrinkles. Botox A does not cause persistent changes at the nerve terminals and targeted muscles. In general, it does not cause any long-term adverse or side effects in the field of dermatology.[1]

Indication: In the field of dermatology, Botox is generally injected into the muscles of facial expression. Most of these muscles are attached to soft tissues rather than bones, and by contracting, they pull across the skin to give facial expressions. In esthetics, Botox is used for reducing glabellar frown lines, crow's feet at the side of the eyes, horizontal forehead creases, wrinkles around the mouth, nasolabial folds and smoothing out neck and chest/cleavage wrinkles. It also can be used to elevate the eyebrows and treat problems such as hyperhidrosis, lichen simplex, pompholyx (dyshidrotic eczema) and acne vulgaris. Botox cannot be used to prevent other signs of aging such as dry skin, pigmentation disorders and vascular abnormalities.[1]

Contraindication: Contraindications with the use of Botox include patients with myasthenia gravis, amyotrophic lateral sclerosis, multiple sclerosis, Eaton Lambert syndrome, women who are pregnant and breastfeeding, neonate and children, patients with focal and systemic infections, patients who are hypersensitive or allergic to Botox and patients who had previously undergone lower eyelid surgery.[1]

3. PHARMACOLOGY

MECHANISM OF ACTION

1. Working knowledge of BT-A pharmacology is necessary to understand complications of treatment and contraindications. BT is a polypeptide comprises a protein molecule with a heavy and light chain held together by a heat-labile disulfide bond. Disruption of disulfide bond inactivates the neurotoxin; so BT storage at the correct temperature is necessary. Reconstitution should be carried out carefully to preserve the integrity of both the chains.

2. BT blocks the release of Acetylcholine at the skeletal neuromuscular junction and induces paralysis by inhibiting transmission of a nerve impulse across the synaptic junction to the motor end plate. The chemodenervation results in weakness or classic paralysis. The BT heavy chain attaches to the nerve membrane which allows the light chain transportation to its site of action, that is, the protein complex. The light chain enzyme then cleaves the protein specific to the particular neurotoxin. Hence, neuromuscular transmission ceases, and reversibly target muscle atrophies.

3. If the handling of BT is not proper, the fragile bond splits and makes the molecule ineffective. The binding of a molecule is permanent to the motor end plate, and it requires 24–48 h for therapeutic action. This delay is due to the time required to deplete acetylcholine storage in the presynaptic motor end plate. Although

binding is permanent paralytic effect persists only for 2–6 months. The reason for this reversal is the reestablishment of neurotransmitter pathway due to new axonal sprouts formation. This neurogenesis process allows complete recovery of transmission pathway which results into the muscle function.

4. BT-B acts on the different cytoplasmic complex. The light chain of BT-B molecule cleaves vesicle-associated membrane protein. BT-B is effective with cervical dystonia and those resistant to BT-A.[3]

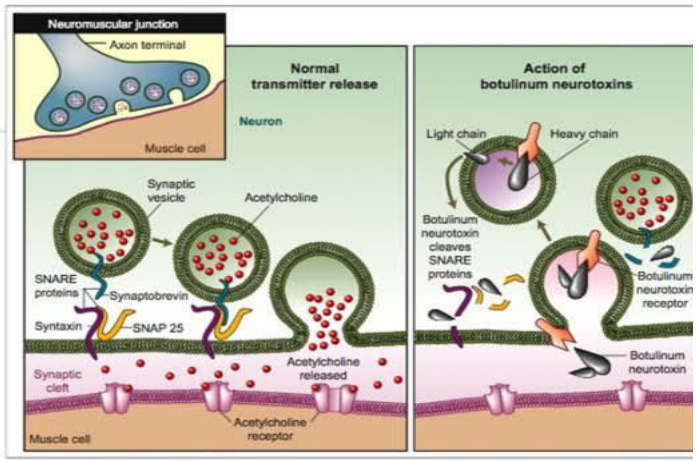

Fig:3 Mechanism of action

4. CLINICAL USE OF BOTULINUM

BT used successfully in cosmetic and noncosmetic indications. The cosmetic indications such as crow's feet, vertical and horizontal frown, wrinkles on the nose, upper lip rhytids, nasolabial fold, horizontal and vertical neck bands, scar management, and pebbly chin.The noncosmetic indications are migraine, strabismus, hemifacial spasm, bruxism, blepharospasm, spasmodic torticollis, postfacial nerve palsy synkinesis, hyperhidrosis, and esophageal achalasia.

The clinical effects of Botox are seen on the first to the fourth days after injection, followed by 1–4 weeks of maximum effect, which will resolve after 3–4 months. In order to prolong the effects of Botox from six months to one year, the treatment should be repeated for one year or more.The duration of Botox effect varies among individuals due to differences in muscle arrangements, meaning that different individuals may require different doses of Botox. The effect will last up to 120 days.

Botulinum toxin is currently approved for the following therapeutic applications:

- Blepharospasm (spasm of the eyelids).
- Idiopathic rotational cervical dystonia (severe neck and shoulder muscle spasms).
- Chronic migraine.
- Severe primary axillary hyperhidrosis (excessive sweating).
- Strabismus (crossed eyes).
- Post-stroke upper limb spasticityTrusted Source.
- Detrusor (bladder wall muscle) overactivity - causing urinary incontinenceTrusted Source.
- Overactive bladder.
- Hemifacial spasm.
- Glabellar lines (frown lines between the eyebrows).
- Canthal lines (crow's feet).

Botulinum toxin is also used off-label (not approved) for:

- Achalasia (an issue with the throat that makes swallowing difficult).
- Anal fissure and anismus (dysfunction of the anal sphincter).
- Sialorrhea (producing too much saliva).
- Allergic rhinitis (hay fever).
- Sphincter of oddi (hepatopancreaticTrusted Source) dysfunction (causes abdominal pain).
- Cerebral Palsy.
- Oromandibular dystonia (forceful contraction of the jaw, face, and/or tongue).
- Laryngeal dystonia (forceful contraction of the vocal cords).

Botulinum toxin is sold commercially under the names:

- Botox, Vistabel, Botox cosmetic (OnabotulinumtoxinA or botulinum toxin type A)
- Dysport (AbobotulinumtoxinA or botulinum toxin type A)
- Bocouture, Xeomin (IncobotulinumtoxinA or botulinum toxin type A)
- Myobloc (RimabotulinumtoxinB or botulinum toxin type B).

Fig:4 Botox Treatment uses

5. PROCEDURE STORAGE AND TECHNIQUES

BOTOX Cosmetic is supplied in single-use 50 Units and 100 Units per vial. Prior to intramuscular injection, reconstitute each vacuum-dried vial of BOTOX Cosmetic with sterile, preservative-free 0.9% Sodium Chloride Injection USP . Draw up the proper amount of diluent in the appropriate size needle and syringe to obtain a reconstituted solution at a concentration of 4 Units/0.1 ml and a total treatment dose of 20 Units in 0.5 ml for glabellar lines, 24 Units in 0.6 ml for lateral canthal lines, and 40 Units in 1 ml for forehead lines and glabellar lines. Then slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix BOTOX Cosmetic with the saline by rotating the vial. Record the date and time of reconstitution on the space on the label. BOTOX Cosmetic should be administered within 24 hours after reconstitution. During this time period, reconstituted BOTOX Cosmetic should be stored in a refrigerator (2° to 8°C). BOTOX Cosmetic vials are for single-use only. Discard any remaining solution after administration.[5]

The cosmetologists should have a thorough knowledge of the muscles of the area to be injected. The beginner should mark the injection sites with a washable skin marker. It is important to follow aseptic precautions. During injections, it is vital to avoid nerve, vein, and artery complex in the region of glabella. It is better to know the surface anatomical landmarks such as supraorbital nerves for injection on the glabellar area.

The injection in the forehead region usually starts from frontalis zone. During injection, assess the bulk of muscle by asking the patient to frown, then relax and inject at the noted point. Do not touch the periosteum, take care to point the needle away from the danger area, avoid pointing toward orbital septum while injecting at the lateral canthus. Sometimes, it is useful to hold the muscle between two fingers in the glabellar area. In lateral orbital skin, spread the skin to observe the orbital veins clearly during injection. Look carefully to avoid superficial veins.[6]

DOSE:

• Treat forehead lines in conjunction with glabellar lines to minimize the potential for brow ptosis1

• The approved dose for treatment of forehead lines (20 Units) in conjunction with glabellar lines (20 Units) is 40 Units1

• For simultaneous treatment of all 3 areas, the dose is 20+24+20 Units (20 Units for forehead lines, 24 Units for lateral canthal lines, and 20 Units for glabellar lines) for a total dose of 64 Units1

40-Unit dose provides efficacy without an increase in side effects, compared with a lower dose.

Forehead lines	20 units
Lateral canthal lines	24 units
Glabellar lines	20 units

Table no: 1

Dilution table:

• BOTOX® Cosmetic is supplied in 100-Unit and 50-Unit single-use vials for reconstitution

• BOTOX® Cosmetic should be reconstituted with sterile, preservative-free 0.9% sodium chloride injection USP

Note: once open and reconstituted, use within 24 hours, because product and diluent do not contain a preservative. During the 24 hours, BOTOX® Cosmetic should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F). Vials are for single-use only.

	Diluent added (preservative free 0.9% sodium chloride injection, usp)	Resulting dose (units per 0.1ml)
100units vial	2.50 ml	4.00units
50units vial	1.25ml	4.00units

Table no: 2

Fig: 5 Dose Dilution

6. PATIENTS SELECTION

Patients with dynamic wrinkles demonstrate the most dramatic improvements from botulinum toxin injection and are ideal candidates for treatment *(Figure A*[49]*)*. Patients with static wrinkles that are visible at rest are also candidates *(Figure B*[49]*)*, but results are slower and patients may require two or three consecutive botulinum toxin treatments for significant improvements. [49] Deep static lines may not fully respond to botulinum toxin injection alone and may require combination treatment with dermal fillers or other cosmetic procedures to achieve optimal results. Setting realistic expectations at the time of consultation is important for patient satisfaction and success with botulinum toxin treatments. Contraindications to botulinum toxin injection include keloidal scarring, neuromuscular disorders (e.g., myasthenia gravis), allergy to constituents of botulinum toxin product, unrealistic expectations, and body dysmorphic disorder .[50]

BOTOX® Cosmetic (onabotulinumtoxin A) is indicated in adult patients for the temporary improvement in the appearance of:

- moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity

- moderate to severe lateral canthal lines associated with orbicularis oculi activity

- moderate to severe forehead lines associated with frontalis activity BOTOX® Cosmetic (onabotulinumtoxinA) dose is dependent on the area(s) being treated. BOTOX® Cosmetic dilution and reconstitution processes are the same for moderate to severe forehead lines, lateral canthal lines, and glabellar lines.

Fig: 6 Patient selection

Fig: 7 Quantity selection of botox on various parts of face.

For moderate to severe forehead lines

When identifying the location of the appropriate injection sites in the frontalis muscle, assess the overall relationship between the size of the subject's forehead and the distribution of frontalis muscle activity.

Locate the following horizontal treatment rows by light palpation of the forehead at rest and maximum eyebrow elevation:

• Superior margin of frontalis activity: approximately 1 cm above the most superior forehead crease

• Lower treatment row: midway between the superior margin of frontalis activity and the eyebrow, at least 2 cm above the eyebrow

• Upper treatment row: midway between the superior margin of frontalis activity and lower treatment row.

Inject 4 Units/0.1 ml of reconstituted BOTOX® Cosmetic into 5 sites in the frontalis muscle for a total of 20 Units/0.5 ml. Place the 5 injections at the intersection of the horizontal treatment rows with the following vertical landmarks:

• On the lower treatment row at the midline of the face, and 0.5–1.5 cm medial to the palpated temporal fusion line (temporal crest); repeat for the other side

• On the upper treatment row, midway between the lateral and medial sites on the lower treatment row; repeat for the other side

For moderate to severe glabellar lines

• Inject 4 Units/0.1mL into each of the 5 sites—2 in each corrugator muscle and 1 in the procerus muscle—for a total dose of 20 Units1 to reduce the risk of ptosis:

• Avoid injection near the levator palpebrae superioris, especially in those patients with larger brow-depressor complexes1

• Lateral corrugator injections should be placed at least 1 cm above the bony supraorbital ridge1.

• Ensure the injected volume and dose are accurate and, where feasible, kept to a minimum.

• Do not inject botulinum toxin closer than 1 cm above the central eyebrow.

For moderate to severe lateral canthal lines1

• Injections should be given with the needle bevel tip up and oriented away from the eye1.

• Inject 4 Units/0.1ml into each of the 6 sites (3 injections per side) for a total dose of 24 Units

1. Two approved injection patterns 1. If lines are both above and below the lateral canthus:

• First injection: at least 1.5 cm to 2.0 cm temporal to the lateral canthus and just temporal to the lateral orbital rim.

• Second injection: 1.0 cm to 1.5 cm above the first injection site and at an approximate 30° angle medially

• Third injection: 1.0 cm to 1.5 cm below the first injection site and at an approximate 30° angle medially.

2. If lines are primarily below the lateral canthus:

• First injection: at least 1.5 cm to 2.0 cm temporal to the lateral canthus and just temporal to the lateral orbital rim.

• Inject along a line that angles from antero inferior to super posterior.

• Ensure that the most anterior injection is lateral to a line drawn vertically from the lateral canthus3

• Remember to keep the most inferior injection superior to the maxillary prominence.

CONCLUSION : Based on this review, it can be concluded that Botox is a good safe medication in reducing facial wrinkles. There are several issues regarding side effect and complication following the injection. However, there are several techniques to reduce side effect and complication rate after the injection. Physicians should consider the suitability of BTX-A for elderly patients, taking into account the etiology of their wrinkles, skin fragility, facial anatomy, concomitant medications and medical conditions, risk of adverse effects and the likelihood of treatment benefit. Although BTX-A has a low perceived risk of side effects, older patients may be more susceptible to these effects. The benefit from BTX-A treatment is also questionable since wrinkles in older people are more likely to be caused by factors other than repeated muscle contraction. Precautions such as a obtaining a full medication and medical history, beginning with low doses, and proper injection technique are especially important for optimal outcomes in elderly patients who are deemed to be good candidates for BTX-A cosmetic injections. A fixed measurement device such as the dose disc applied in this study can assist injectors in designing an injection pattern that is both safe and effective for a variety of patients as long as a standard technique is followed. Future studies assessing other disc models for different doses and different injection methods are needed, with the goal of establishing a longer duration of the effect and devising similar templates for other facial areas.

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