

Botulinum Toxin Application in Facial Esthetics and Recent Treatment Indications (2013-2018)

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INTRODUCTION

Ever-changing perception of beauty from childhood to old age is changing with the revolution in cosmeceuticals science. Esthetics is an individual's perception since time immemorial. Standards of beauty have changed through centuries with increased awareness about esthetics. The youthfulness despite advancing age includes smooth, charming skin without skin folds, volume loss, and skin laxity.^[1] According to Ayurveda aging is defined as “to become

ABSTRACT

Background: Ever-changing perception of beauty from childhood to old age is changing with the revolution in cosmeceuticals science. Esthetics is an individual's perception since time immemorial. Standards of beauty have changed through centuries with increased awareness about esthetics. The face remains main source of information for identification and discrimination. It constitutes a structural ground for many nonverbal messages including the emotional state of a person, so the proverb “Face is an index of mind” holds good. The wrinkles and laxity are considered to be one of the factors for aging. Hence, escalating demand for cosmetic treatment to reduce facial wrinkles and laxity has stimulated us to search for published literature for nonsurgical techniques for enhancement of facial beauty. The review analyzed the published data to provide narrative basic review in a concise way to the beginners, clinicians, and students.

Materials and Methods: We have adopted search criteria using keywords: Botox, Botulinum toxin, incobotulinumtoxinA, esthetics, face, uses of Botox, with various Boolean operators and or in title, and abstract using PubMed search engine. The database search limited to PubMed only from January 2013 to June 2018.

Results: Various search results have been appended as annexures at the end of the article for further reference for the readers. Finally, 17 references were selected to write narrative review to meet our objectives.

Conclusion: The advancing front in the use of toxins is an emerging science for the beautification of a face. Botox exploded in to market because of efficacy, tolerability, and minimally invasive nature. The present review gives brief about the history of Botulinum toxin, types, mechanism of action, clinical indications, preparations, storage, and technique for various uses with a brief note on patient selection, contraindications, and complications.

KEYWORDS: *Aging, botulinum toxin, cosmetics, esthetics, face, noninvasive procedure, wrinkles*

old by the act of wearing out” which is a synonym for “Vardhakya.”^[2] Aging is an inevitable biological process, in which both intrinsic and extrinsic determinants led progressively to a loss of structural integrity and physiological function.^[2] The desire to look younger and in turn, vital has been a lure to

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humanity for ancient times, though aging remains as a rule and a fact of life.^[3]

The face remains main source of information for identification and discrimination. It constitutes a structural ground for many nonverbal messages including the emotional state of a person, so the proverb “Face is an index of mind” holds good. The wrinkles and laxity are considered to be one of the factors for aging. The wrinkles in hyperfunctional muscles sometimes may be misinterpreted, when these types of habitual repeated contraction accompanied by a lack of shortening of skin which will produce a wrinkle.^[4] The pursuit of youth and beauty has undergone a resurgence of interest as evidenced by increased visits of people to cosmetology clinics. The field of esthetics is expanding with advances in the area of facial rejuvenation. In the present era, multiplicity of lasers to cosmeceuticals and other innovations are complemented to the armamentarium of cosmetologist. The limitations and strength of these various tools must be understood by the physician and the patient; so that one can tailor the most effective treatment plan appropriately.^[5]

Escalating demand for cosmetic treatment to reduce facial wrinkles and laxity has stimulated the search of published literature for nonsurgical techniques for enhancement of facial beauty. The advancing front in the use of toxins is an emerging science for the beautification of a face. This miracle poison is enormously used nowadays, after the Food and Drug Administration approval in 2002 by the Government of the United States.^[6] Botox exploded on to market because of efficacy, tolerability, and minimally invasive nature.^[7] The present review gives brief about the history of Botulinum toxin (BT), types, mechanism of action, clinical indications, preparations, storage and technique for various uses with a brief note on patient selection, contraindications, and complications. The review also briefs few published literature on the use of Botox in various facial esthetics procedures.

MATERIALS AND METHODS

The search using Botox (All Fields) OR OnabotulinumtoxinA (All Fields) AND (“face” [MeSH Terms] OR “face” [All Fields]) AND (“2015/01/01” (PDAT): “2018/12/31” (PDAT)) AND “humans” [MeSH Terms]) in PubMed search engine from January 2013 to December 2018. We have even activated additional filters such as number of years to recent 5 years, clinical trials, published in English language only with human studies and clinical trials, and reviews have been considered for writing the narrative review. All remaining data excluded from the writing purpose. The finalized articles were downloaded from various sources

for reading completely and analyzing the necessary data for extraction and synthesis of narrative review.

RESULTS

Various search results have been appended in Annexure 1 showing references of total 1832. The results have been refined using filter of recent 5 years (2013–2018) period yielded 556 published articles [Annexure 2]. The search further activated additional filters of only English and humans resulted in 325 published articles [Annexure 3]. Later, the search has been restricted to only reviews yielded 120 results [Annexure 4]. We have activated one more additional filter of clinical trials which yielded 51 results [Annexure 5]. All the resulted references and abstracts have been screened for usefulness to write a narrative review was identified. Finally, the search criteria of Botox (All Fields) OR OnabotulinumtoxinA (All Fields) AND (“face” [MeSH Terms] OR “face” [All Fields]) with time duration was activated to find the results [Annexure 6]. Of these final 63 references, the abstract has been read by the team members for suitability of inclusion in the study; and assorted the articles for writing a narrative review. Table 1 shows references used for writing the review

Table 1: Selected recent and few past studies involved for revision of esthetic and nonesthetic uses of Botulinum toxin

Reference number	Author	Year	Use
15	Paulo Keiki R <i>et.al.</i>	1996	Fronto-glabella Wrinkles
16	Andrewblitzer <i>et.al.</i>	2001	Facial lines and wrinkles
18	Achih H <i>et.al.</i>	2003	Altering brow contour
19	Benjamin A <i>et.al.</i>	2003	Glabellar rhytids
20	David W <i>et.al.</i>	2003	Lateral periorbital rhytids
22	Makram Ziadeuse <i>et.al.</i>	2013	Management facial wounds
31	Chen H <i>et.al.</i>	2018	Treating sunk scar
32	Jones DH <i>et.al.</i>	2017	Glabellar frown lines
33	Solish N <i>et.al.</i>	2016	Forehead lines
34	Hsu Ak <i>et.al.</i>	2017	Chin projection modification
39	Erickson BP <i>et.al.</i>	2015	Periorbital and midfacial areas
41	Steinsapir KD <i>et.al.</i>	2015	Forehead lift
43	Charles PD	2004	Noncosmetic uses
44	Awan KH	2017	Noncosmetic uses
46	Halpern L <i>et.al.</i>	2016	Noncosmetic uses
47	Vikelis M	2018	Noncosmetic uses
48	Bolshinsky V	2018	Noncosmetic uses

briefly to meet out the criteria set. Out of all search mentioned above references, our team members selected results only related to esthetics and humans; which have been considered to write a narrative review to provide the necessary outlook for the intended users.

DISCUSSION

The advancing front of the use of toxins is an emerging science for the beautification of a face. This miracle poison is enormously used nowadays after the Food and Drug Administration approval in 2002 by the Government of the United States. Botox exploded on to market because of efficacy, tolerability, and minimally invasive nature. The discussion has been divided into history, types of Botox, mechanism of action, clinical scenarios for use, preparation and storage, selection of patients, indications, and contraindications.

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.^[8] 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.^[8] 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 X). In 1989, Ipsen pharmaceuticals bought Porton chemicals and are the only commercially available forms of Botulinum toxin (Dysport)[®].^[8]

Dr. Allen Scott performed a first clinical test in 1978 using type-A BT.^[8] 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.^[9] 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.^[10]

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.^[8]

MECHANISM OF ACTION

Working knowledge of BT-A pharmacology is necessary to understand complications of treatment and contraindications.^[11] 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.^[8,11] Reconstitution should be carried out carefully to preserve the integrity of both the chains.^[8,11] 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 chemodeneration results in weakness or classic paralysis.^[9,12,13] 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.^[8] 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.^[14]

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.^[8]

CLINICAL USE OF BOTULINUM TOXIN

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.^[7,15-42] The noncosmetic indications are migraine, strabismus, hemifacial spasm, bruxism, blepharospasm, spasmodic torticollis, postfacial nerve palsy synkinesis, hyperhidrosis, and esophageal achalasia.^[43-48]

PREPARATION, STORAGE, AND TECHNIQUE

BT is delivered in an insulated glass vial as 100 units of freeze-dried powder. The manufacturer's guidelines should be followed very strictly to prevent denaturation and maintain a maximum efficacy. The storage before reconstitution either frozen at -5° or in a refrigerator at 2° – 8° ; once reconstituted must be stored at 2° – 8° . If the clinic is not having a refrigerator thermos flask or vaccine transporter can be used. Companies such as Allergan do not recommend this type of storage. Dysport® comes in a plastic hinged box which contains two glass vials. Ipsen recommends the use of Disport® within 8 h and should not be frozen.

BT reconstitution should follow the standard aseptic precautions. The product is vacuum sealed, so air can be injected to avoid the rapid constitution. Saline must not be pushed into the vial to prevent agitation of solution mechanically. Rotating of the vial assists the gentle reconstruction. After reconstitution, during transport, cold pack insulation box should be used or else, it should be reconstituted after the journey as agitation denatures toxin and reduces the duration of action.

BT injections are used intramuscularly and not subcutaneous unless specifically stated. Injections around dangerous areas require careful analysis of the dose and depth of the injection. Intramuscular placement is essential for maximum effect and control, but in areas like corner of the mouth, subcutaneous treatment can be considered.

The dose required for cosmetic use has been discussed and established independently by many researchers based on their experiences^[22-41] [Table 1]. Review of literature provides more information on dosage preferences by practitioners.^[42] BT is potent and very expensive, so each drop must be used cautiously even 0.0125 mL is effective in certain areas.^[8] The comparison of the average doses of different BT products for different esthetic purposes showed a significant deviation from accepted 1:1 equivalence coefficients for OnaBTXA: IncoBTXA and 1:2.5 for OnaBTXA: AboBTXA, depending on a particular area of the face.^[42] Hence, the clinician can follow national guidelines with their experience during various esthetic procedures.

The cosmetologists should have a thorough knowledge of the muscles of the area to be injected.^[23] 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.^[23] 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.^[24-26] 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.^[23] Slow insertion during injection significantly reduces the pain perception by minimizing mechanical stimulation.^[27,28] Few authors reconstitute with lidocaine, but the efficacy of BT-A has not been tested.^[8] Postinjection, the patient should be asked to press on the site of injection with a tissue which minimizes bruising. If any bruise occurs, an ice pack should be used. Makeup can be used as a camouflage before the patient leaves the hospital. Few believe that ptosis may happen because of untoward diffusion due to flying or lying down after the treatment.^[8] Usually, the duration of appointment lasts for a maximum of 10 min excluding counseling visits. It is advisable that nurse may prepare the patient that reduces time spent with the practitioner.

SELECTION OF PATIENT

During esthetic procedures, it is very much advisable to understand the requirements of patients. Few patients should be assessed thoroughly when they do not have a clear idea of their need and good esthetic sense. They might have motivated because of their friends or parents advice. If this is the situation, the clinician should not commit. The golden rule for the use of Botox is a perceivable pleasure after their expenditure.^[8] The patient trust in the clinician will reduce where the patient think their demands has not been met. In such a scenario, it is better for the clinician to refuse the treatment. If the patient is unhappy; the procedure cannot be reversed in a week. Hence, it is essential to listen to the complaint and decide quickly whether the patient can be treated with BT or not. The careful psychological assessment is essential. Spend time with a patient by providing verbal and written information if the patient seems suitable. Always examine the patient closely and discuss likely outcome of the injection. Make sure the patient understands fully, before the patient is taken for injection. The preoperative photography is the must.

The clinician should decide before the injection whether alone BT will eliminate or reduce, or prevent further rhytids or any other adjunctive treatments is required. If so, a patient should be conveyed the fact and the outcome.^[26] Observe the patient face, neck, and hands while talking and in action.

The clinical examination before consideration for injection is as follows: look for a general skin conditions such as sun damage, pigment spots, and tonicity of the skin. The investigation of the cardiovascular system, skin perfusion, and the overall tone is necessary.^[27] Brow position, change with expression should be observed. Crow's feet at rest and in motion should be examined along with its extension toward perioral lines when smiling. Hooding should be examined and its disappearance when the patient lifts the brow. All these should be reviewed at rest and in action for successful execution.

INDICATIONS FOR TREATMENT

Wrinkles of the face

If the dynamic wrinkles are present with frowning and smile it can be treated.^[33] If the patient has wrinkles at rest and sun damage, and elderly patient better to take precautions because it will reduce lines, but will not eliminate them.^[41]

Glabella rhytid

If it is dynamic, the treatment will be successful but if it is at rest caution, the patient as it may not be eliminated completely.^[32] If the patients have a heavy bruise after treatment which may increase medial sagging. Eyebrow and lash distance is an important factor, as it may cause tired appearance if the distance is less. In asymmetrical brows motion, the results of treatment will be asymmetrical. If the frontalis is active, the procedure leads to lateral brow to elevate and creates unattractive peaking of eyebrows.

Horizontal rhytids

If the patients lash – brow distance is good at rest will do well at treatment. In case of high eyebrows, relaxing the horizontal rhytids will prevent high resting tone of brows.^[38,39]

Crow's feet

Wrinkles in action are ideal for treatment, but wrinkles at rest may require modification. Wrinkles extending over zygomatic arch will need more care which usually seen in older patients and creates Mickey Mouse appearance. Hooding of lateral eyebrows will remain same even after the treatment which should be explained to the patient that it may require adjunctive therapies.^[37]

Masseteric hypertrophy

Hypertrophy of the masseter can create a square face of the lower third of the face and convey an impression of heaviness to the face. The square face appearance gives a masculine look. So, many of the female patients wish to reduce the same without surgical intervention. BT provides better noninvasive treatment.^[37]

Many more uses of BT have been noted in dentistry such as hyperactive mentalis, nasolabial furrow, hyperactive

upper lip, and so. The activity can be reduced, and facial harmony can be brought during the action by use of BT injection.^[24,25,39]

The review provided mainly outline and brief about esthetic uses of BT in the maxillofacial area. The knowledge of BT for the clinician is essential to educate the patient and provide insights into esthetic treatment. Increased awareness of esthetics among public, made the necessity for learning and practice of esthetic procedure by a dentist which is increasing because of noninvasive nature of pharmacopeia. BT is becoming boon for the practicing dentist with thorough knowledge of anatomy and indications, contraindications of use of BT successfully without any undue complications. In this review, we have not discussed noncosmetic uses of BT-A which can be read elsewhere in the published literature^[43-48] [Table 1].

CONTRAINDICATIONS

Contraindications of BT are pregnancy, breastfeeding, neuromuscular junction disorders (myasthenia gravis), amyotrophic lateralizing sclerosis, myopathies, and drug interactions.^[36]

CONCLUSION

The success of BT treatment depends on patient satisfaction despite good results. It is better to ask ourselves will this make a patient happy; if not, then better to reassess the patient whether the patient is suitable for BT or not. The patient factors such as identification and avoidance of low intelligence, unreasonable expectations, depression, and dysmorphophobic patients are crucial factors for successful management of esthetic patients. Knowledge of anatomy, proper technique, and exposure for different scenarios of treatment using BT is much essential for successful treatment.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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ANNEXURE

Annexure 1: Showing search result of 1832 published articles on Botox in all fields in PubMed search engine without any filters activated. Download link: http://www.jispcd.org/articles/2019/9/2/images/JIntSocPreventCommunitDent_2019_9_2_99_256006_sm2.pdf

Annexure 2: Activation of filter published in the past 5 years' duration yielded into 556 published articles on Botox in all fields. Download link: http://www.jispcd.org/articles/2019/9/2/images/JIntSocPreventCommunitDent_2019_9_2_99_256006_sm3.pdf

Annexure 3: Activation of filters English and humans resulted 325 published articles. Download link: http://www.jispcd.org/articles/2019/9/2/images/JIntSocPreventCommunitDent_2019_9_2_99_256006_sm4.pdf

Annexure 4: Activation of filters reviews resulted 120 published articles. Download link: http://www.jispcd.org/articles/2019/9/2/images/JIntSocPreventCommunitDent_2019_9_2_99_256006_sm5.pdf

Annexure 5: Activation of clinical trial filter resulted in 51 results. Download link: http://www.jispcd.org/articles/2019/9/2/images/JIntSocPreventCommunitDent_2019_9_2_99_256006_sm6.pdf

Annexure 6: Result of search criteria Botox (All Fields) OR OnabotulinumtoxinA (All Fields) AND (“face” [MeSH Terms] OR “face” [All Fields]) with 5 years yielded 63 published articles. Download link: http://www.jispcd.org/articles/2019/9/2/images/JIntSocPreventCommunitDent_2019_9_2_99_256006_sm7.pdf