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REVIEW ARTICLE

Complications of Botulinum toxin A: An update review

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Abstract

Cosmetic surgery procedures have increased manifolds all over the world owing to the ever-increasing demand of people to look beautiful and young. Injectable treatments like botulinum toxin are becoming more popular owing to their rapid, well-defined, and lasting results for the reduction of facial fine lines, wrinkles, and facial rejuvenation. These emerging treatments are quite safe but can have certain adverse effects. In this article, we have highlighted the complications and side effects of botulinum toxin based on the anatomical location. The possible causes and precautions to prevent these complications are also discussed. The search of literature included peer-reviewed articles including clinical trials and scientific reviews. Literature was identified from electronic databases (MEDLINE/PubMed) through January 2021 and references of respective articles and only the articles published in English language were included.

KEYWORDS
Botulinum toxin A, complications, treatment

1 | INTRODUCTION

Esthetics is a growing field with advances in facial rejuvenation. Botulinum toxins are commonly used in esthetic practice for beautification of a face, that is, the correction of wrinkles and laxity.[1] The botulinum toxin acts by blocking the acetylcholine release at the site of motor endplate causing muscle paralysis.[2,3] Its action involves the selective paralysis of certain muscles but inadvertent paralysis of adjacent or other muscles can cause adverse effects.[4,5] It has been demonstrated that intradermal injection of botulinum toxin can be considered as an effective method for facial rejuvenation.[6,7] Its injection to correct the physical aspects of the aging process is one of the most frequently required esthetic procedures in recent years.[8,9] Although botulinum toxin injections are generally well-tolerated, poor patient satisfaction and/or complications can occur with its use. A systematic review of literature has shown significantly more adverse events with Botulinum toxin A when used for facial rejuvenation as compared to placebo.[10] Patient and physician related factors can contribute to these complications.[11] The reasons of which may include poor knowledge about the facial anatomy and poor injection technique.[12]

The facial anatomy can be broadly divided into three parts: upper third (i.e., forehead, glabellar muscles, and periocular area), middle third, that is, nasal area and lower third of the face (masseter muscle and mandibular area), and neck. Systematic information about the common and specific adverse events associated with botulinum toxins is limited.[12] In this article, we discussed the complications of botulinum toxin A by classifying them according to facial anatomy. General complications irrespective of the site of injection are also discussed.

1.1 | Complications in the upper face

For several years, botulinum toxins have been used for upper face rejuvenation.[13] Botulinum toxin is mainly used in the upper face for correction of wrinkles.[14]

Although rare, complications in this region can occur with use of botulinum toxin. In a retrospective study involving 845 subjects who underwent upper face rejuvenation with 18-point Abobotulinum toxin A, incidence of adverse events was only 2.6%. The most common adverse event in this study was bruise at the lateral canthal part. The other adverse events included blepharoptosis, persistence of eyebrow asymmetry post-touch-up, and headache.[15] Brow ptosis, diplopia, ectropion, lagophthalmos, and xerophthalmia can also occur after botulinum toxin.

1.2 | Brow ptosis

Brow ptosis (Figure 1) is a frequent complication that can arise in the management of the frontalis muscle with botulinum toxin. Weakness of frontalis results in brow ptosis.[12] The incidence of brow ptosis ranges from less than 1%–5%.[16] In a study involving 25 patients with injection of forehead rhytides, 22 had mean brow ptosis of 2.3 mm. Eyelid ptosis was not seen in any case.[17] The causes of brow ptosis include wrong site of injection, high dose, and wrong selection of patients.[16]

Brow ptosis can be prevented by injecting around 2–3 cm above supraorbital margin or at least 1.5–2 cm over the eyebrow. This precaution can spare the frontalis muscle function in the area which prevents drooping and ptosis of the brow.[18,19] In patients with horizontal forehead and glabellar frown lines, glabellar area should be injected alongside forehead, otherwise, brow ptosis can occur owing to the depressor action of glabellar muscles.[19,20] Forehead depressor injection helps to reduce the risk of brow ptosis.[17] Ptosis of the upper eyelid due to migration of toxin is also seen when toxin is used in and around the glabellar region. Toxin can migrate through orbital septum which can cause weakness of the levator palpebrae superioris. This complication is usually observed when toxin is injected in proximity to supraorbital margin in mid-pupillary line or when higher quantities of toxin are used.[20,21] Ptosis can be seen up to 7–10 days post-injection and can last for 2–4 weeks or longer. Lid ptosis is also observed in elderly who have pre-existing dermatochalasis of eyelids and who are unconsciously using the lower fibers of the frontalis muscle to elevate the brow and eyelids. The toxin can cause reduction of this frontalis compensatory action leading to secondary blepharoptosis.[22,23] Apraclonidine 0.5% eye drops can be used to ameliorate the eyelid ptosis by causing contraction of the Mueller's muscle, which is a sympathomimetic elevator muscle of the upper lid, thereby raising the upper eyelid by 1–2 mm. Phenylephrine ophthalmic solution is an alternative if apraclonidine is not available, but its use should be properly monitored owing to the risk of adverse effects like narrow-angle glaucoma.

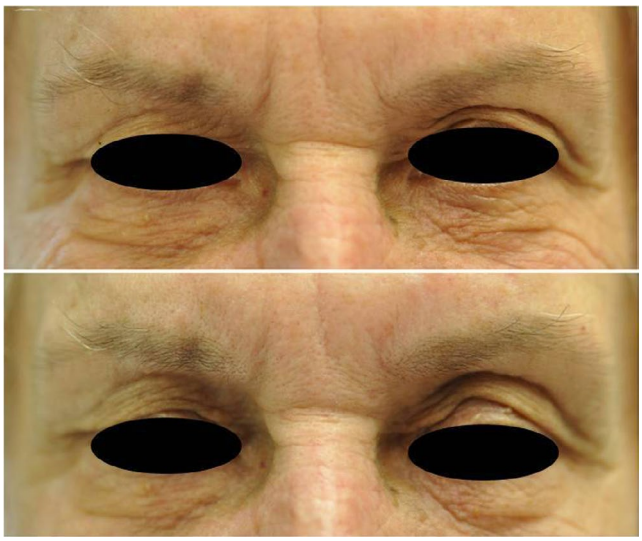

FIGURE 1 Female patient before (above) and after cosmetic treatment (below) with onabotulinum toxin A. Ptosis of the upper eyelids is shown after treatment with injections in and around the glabella. This adverse effect resulted from injecting large volumes of diluted botulinum toxin. It was treated with apraclonidine

2 | DIPLOPIA, ECTROPION, LAGOPHTHALMOS, AND XEROPHTHALMIA

Injection of toxin into lateral can thus can cause side effects like brow ptosis, ectropion, xerophthalmia, diplopia, and lagophthalmos.[19,20] Ectropion results from the inadvertent loss of strength of the lateral orbicularis muscular sling due to inadvertent diffusion of the toxin which can cause secondary complications due to prolonged corneal exposure like secondary dry eye. Ectropion can also occur because of local diffusion of Botox after injection into the lower eyelids.[24] When planning infraorbital orbicularis injections, one should exclude patients with sclera who show pre-treatment or dry eyes because they may worsen with BoNTA treatment.

Occurrence of diplopia after botulinum A toxin injection is not common. A study reported that 1.7% incidents of diplopia with the most identifiable reason of inferior oblique muscle paresis.[25]

Diplopia can appear due to inadvertent diffusion of toxin beyond the orbital septum which can cause weakening of the other extraocular muscles and lateral rectus. Xerophthalmia can be seen if toxin is injected deep into upper lateral periocular area which can affect lacrimal gland secretions. Lagophthalmos can also occur due to the orbicularis oculi sphincteric function loss leading to the inadequate closure of eyelids. Inadvertent loss of orbicularis oculi sphincteric function along with eyelid weakness can appear if toxin diffuses into palpebral part of orbicularis oculi resulting in lagophthalmos. Epiphora can occur due to the toxin-induced weakening of medial palpebral portion of orbicularis oculi which

leads to diminution in the action of lacrimal pump. Such complications can be prevented by subdermally injecting the toxin, and by injecting lateral to a vertical line passing through the lateral canthus.[18,19,23]

patients having orbital fat herniation can develop prominent of pseudo-herniating infraorbital fat pads after lower lid injections with BoTNA and should therefore not be treated with BoTNA until the fad pads had been removed.[26]

3 | ASYMMETRY

Asymmetry is a fairly common side effect occurring due to placement of injection or patient's anatomical variations. A common complication called "Spock" eyebrow (Figure 2) presents as upward curvature of lateral brow resulting due to imbalance caused from the loss of action of central frontalis and unopposed action of lateral frontalis which elevates the brow tail. This complication may be corrected by injecting some extra toxin into the active area of muscle.[19] It is also a common adverse effect seen in patients over 65–70 years who are treated for glabellar lines. Most of these patients possess a lower asymmetric brow on one side, along with a lower position of upper eyelid on the ipsilateral side. The compensatory brow lift will lead to unobstructed vision, but when such patients are treated with botulinum toxin resulting in weakening of the lower frontalis fibers, the patient's compensatory brow lift is disrupted. With lowered brow height, there is an apparent droop in the upper eyelid. This can

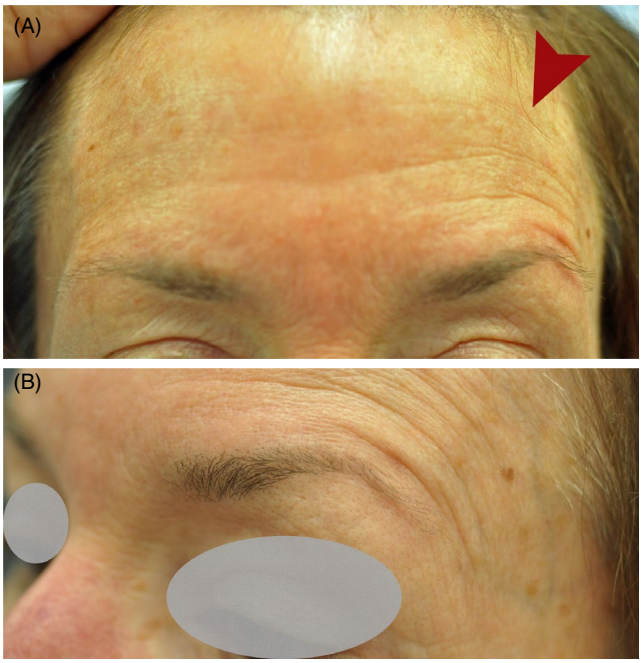

FIGURE 2 (A) "Spock" left eyebrow, that is, raised eyebrow tail, is shown. It can be caused by undertreating elevators in the outer half of the forehead (arrow). (B) Bundles of lateral frontalis muscle that caused this adverse effect are shown. Placing a few units of toxin to the lateral frontalis on the affected side corrects the over-elevation of the brow tail

be prevented by carefully examining and noting and accounting for the baseline asymmetry before injection.[27] Another form of asymmetry is iatrogenic asymmetry which arises when the equivalent dose is not injected on the contralateral side, improper diffusion of the toxin into the muscle fibers, or when some fibers of the muscle are thicker or stronger than the other side. This form of asymmetry can be easily managed by injecting a few additional units into the affected muscles.[21]

4 | COMPLICATIONS AFFECTING MIDDLE FACE

Scope for use of botulinum toxin in facial rejuvenation is widened to cover mid and lower face and neck. However, these areas are less common sites of injection with botulinum toxin than the upper face. Diffusion of toxin and accidental injection in adjacent musculature can be the causes of complications.[28] Lip asymmetry, lip ptosis, and changes in facial expression are the complications with botulinum toxin affecting middle face.

5 | ASYMMETRY AND LIP PTOSIS

Lip asymmetry and ptosis are rare complications that are seen if toxin is injected below upper margin of zygomatic arch, or along lower portion of nasal sidewalls thereby inadvertently acting upon upper lip elevators such as the levator labii superioris alaeque nasi and the levator labii superioris.[29] Injection of higher doses into the upper lip can lead to many functional complications like inability to articulate certain letters, sound articulation, and pronunciation of certain phonemes. There can be the development of inability to close the lips firmly which can cause salivary, fluid, and food incontinence. Inability to pucker the lips may persist for up to one month. An overtreatment of the mentalis due to a high dose of toxin can immobilize the mentalis thereby causing an inability to bring lower lip firmly against teeth, leading to involuntary dribbling while drinking and drooling of fluids from corners of mouth.[30,31] Finally, migration of toxin after mentalis injections into the adjacent depressor labii inferioris (DLI) can lead to the inability of lowering the corner of the lip on the ipsilateral side.[32]

6 | CHANGES IN FACIAL EXPRESSION

Facial expression changes like unnatural smile, smile limitation, altered facial appearance, loss of pre-existing dimple, sunken cheek, and sunken temporal fossa have been reported when larger quantities of toxin are injected like in masseter hypertrophy. These changes usually appear within 2–4 weeks and recover in 1–2 months and have been attributed to abnormal diffusion of the toxin into the surrounding muscles. Such complications can be prevented by placing the toxin at a deep level and by keeping it at least

1 cm from the anterior border of the masseter muscle. Aggravation or appearance of nasal lines following glabellar BoNTA can be seen on smiling, known as the "Botox sign." This can be corrected by injection of small doses laterally into the levator nasi muscle.[33]

6.1 | Complications affecting lower face

The treatment of horizontal lines and vertical neckbands with botulinum toxin is a safe modality, but complications are also common. Hoarseness, dysphagia, and neck weakness can occur after injection of botulinum toxin. As the muscles beneath neckbands are responsible for phonation, neck flexion and deglutition, deeper injection, or higher doses of toxin can lead to dysphagia, xerostomia, neck weakness, and dysarthria.[34] In a study among patients with cervical dystonia, dysphagia was reported in 27% patients and pain during swallowing in 5.1% patients.[35]

These complications are more common in older patients as they usually require a higher dose of the toxin and as they have a reduced soft-tissue support in neck, the toxin can easily penetrate the deeper muscles of the neck leading to these complications. A few patients may complain of difficulty in head lifting and keeping it erect and still. These complications are rare and usually take 3–4 weeks to recover. Inadvertent effect on sternocleidomastoid muscle by BoTNA can cause a floppy neck.[36]

Botulinum toxin for the masseter hypertrophy can cause an altered function of temporomandibular joint which may present as a difficulty in mouth opening. Masseter injection can cause a reduction in masticatory force which can lead to masticatory fatigue, reduced bite force, reduced force of mastication, decreased masticatory function, and difficulty in chewing hard foods which usually recover in 3–8 weeks and return to the normal levels by 12 weeks.[37]

6.2 | General complications

6.2.1 | Injection site complications

These include erythema, local edema, and pain at the site of injection and adjacent sites. A retrospective study (n = 89) with the use of BoNT for the treatment of dystonia with mean follow-up period of 18.5 years reported injection site-related adverse events in 19% of the visits. [38] A study reported that for the cosmetic uses of Botulinum toxin type A, injection site reaction (19%) represents one of the most common non-serious adverse events.[39] Most of these complications are short-lived, minor,[40] and usually do not last more than 24–36 h. Ecchymosis or bruising is another common complication, which can be prevented by use of a small size needle and by closer assessment of superficial vessels, especially around lateral canthus. A transient headache with generalized body aches can be seen after the injection in a few patients which can last for 24–72 h. Serious adverse effects like urticaria, anaphylaxis, dyspnea, and soft tissue swelling are rare, but if they arise, immediate standard treatment should be initiated. Suppurative granuloma at injection site has been reported, which showed no organisms on histochemical staining and tissue culture and which resolved after 6 weeks of broad-spectrum antibiotic therapy.[41] Periocular edema lasting for a few days after periocular injection may also occur. This particular reaction is attributed to lymph stasis caused by weakening of sphincteric pumping function of orbicularis oculi, leading to retention of lymph fluid in the adjacent areas.[42]

6.3 | Prevention of botulinum toxin-related complications

Important causes of adverse events with botulinum toxin injection include poor technique and/or poor anatomical knowledge. Good understanding of the anatomy and functions of facial muscles in addition to knowledge about the products and experience of clinician are determinants of better outcomes.[12,14,43]

During the treatment of upper face, anatomical configuration of frontalis muscle should be considered carefully while selecting the site of injections. Selection of active muscles is important to achieve good outcomes.[12] In order to prevent complications, special examination of periocular area with focus on anthropometrics is required before the injection.[44] Use of botulinum toxin in lower face needs detailed knowledge of anatomy, interactions of muscles and esthetic and potential complications of injection at the wrong site.[13] Critical clinical assessment, appropriate dosing, and pre- and post-procedures recommendations are also essential.[45]

7 | CONCLUSION

Botulinum toxin is a powerful medication that has been used to treat various conditions in recent years. Knowing the anatomic landmarks, muscle function, identifying baseline asymmetry, accounting for potential migration of the toxin, and site-specific precautions can mitigate the incidence of unwanted adverse reactions. In the upper face, low concentrations (large volumes) should be avoided to prevent possible diffusion into the orbital septum. In the lower face, one may inject small number of neurotoxin units superficially to avoid adverse effects such as drooling and asymmetry.

DISCLAIMER

"We confirm that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met and that each author believes that the manuscript represents honest work".

AUTHOR CONTRIBUTIONS

G.K. Review and revising the manuscript. Providing the clinical pictures. M.K. Review and revising the manuscript. M.G. Writing and revision of draft. A.P. Review and revising the manuscript. M.G. Writing, reviewing and revising the manuscript.

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