Toxicon 107 (2015) 120–128

Contents lists available at ScienceDirect

Toxicon

journal homepage: www.elsevier.com/locate/toxicon

Aesthetic use of BoNT: Options and outcomes

Ellen Gendler*, Arielle Nagler

NYU Langone Medical Center, New York, NY, USA

ARTICLE INFO

Article history:
Received 25 August 2015
Accepted 26 August 2015
Available online 11 September 2015

Keywords:
BoNT
Clostridium botulinum
Botulinum toxin
Cosmetic
Crows feet
Pretarsal orbicularis
Forehead lines
Glabellar rhytides
Browlift
Masseter
Mentalis
Nasalis
Gummy smile
Marionette lines
Platysma bands
Bunny lines
Corrugator supercilii
Depressor anguli oris

ABSTRACT

There are a multitude of uses for BoNT in the aesthetic realm. Efficacy has been shown in softening glabellar creases, crows feet, forehead rhytides, and in correcting facial asymmetries, including mild eyelid ptosis. Facial shape can be altered through injections of BoNT into masseter, and smiles can be altered with BoNT. Clinical examples of the above will be shown, as well as adverse outcomes with inaccurate injection techniques.

1. Introduction

Botulinum toxin (BoNT) is produced by various strains of *Clostridium botulinum*, a gram positive, anaerobic, spore-forming rod. BoNT has many beneficial applications in medicine.

In the 1980's, Dr. Alan Scott first began publishing articles on the use of purified botulinum toxin for the treatment of strabismus (Scott, 1980). In 1989, the Food and Drug Administration (FDA) first approved botulinum toxin for the treatment of blepharospasm. Then, in 2002, BoNT received its first cosmetic indication for the treatment of dynamic rhytides of the glabella.

Now, BoNT injections are the most popular cosmetic procedures worldwide (Frevert, 2015a). BoNT can be used to treat cosmetically sensitive areas of the face by improving the appearance of dynamic rhytides caused by muscle contraction. There are several areas and findings commonly treated with BoNT in the upper face (glabella, forehead, brown), mid face (bunny lines, Crow's feet), and lower face (gummy smile, masseter, mentalis, melolabial folds, and neck). This review will discuss the cosmetic uses of BoNT and review complications associated with treatment. Safe and effective treatment with BoNT requires knowledge of facial anatomy as well as techniques to avoid complications. Prior to any treatment with BoNT, the clinician must study the patient's use of muscles of facial expression both actively and at rest.

2. Mechanism of action

There are seven different BoNT serotypes, denoted types A through G (Meunier et al., 2002). The different serotypes of botulinum toxin vary in size, cellular mechanism of action, and method of purification (Carruthers and Carruthers, 2005). The human nervous system is susceptible to only five of the seven types, with type A (BoNTA) being the most potent in humans (Carruthers et al., 2013a).

All types of BoNT block neuromuscular transmission at the presynaptic motor nerve terminal. BoNT travels to the neuromuscular junction, binds to high-affinity pre-synaptic receptors, and is

* Corresponding author.
E-mail address: ellengendlermd@gmail.com (E. Gendler).

http://dx.doi.org/10.1016/j.toxicon.2015.08.023
0041-0101/

internalized. BoNT then cleaves a membrane-associated protein responsible for acetylcholine exocytosis. The specific receptors targeted by BoNT vary among BoNT serotypes. For example, BoNTA cleaves the synaptosomal associated protein 25 (SNAP25) and BoNTB cleaves a vesicle-associated membrane protein, synaptobrevin. In the US both BoNT A and B subtypes have FDA approval; however, BoNTA products are the most widely used and the only products approved for cosmetic purposes, and therefore will be then only BoNTA products discussed in this review.

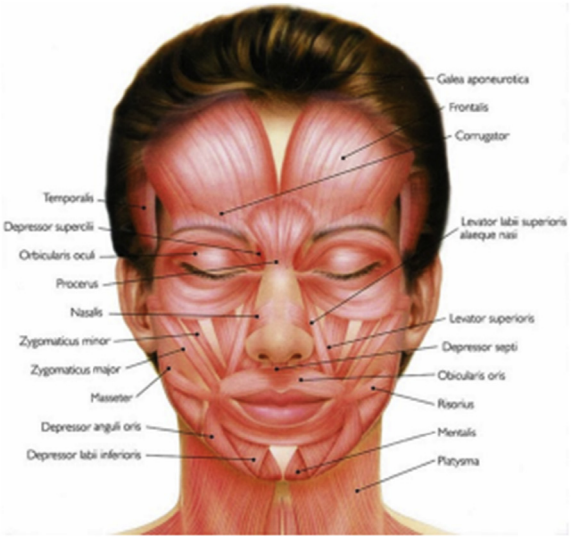
3. Types of botulinum toxin

BoNT formulations used in cosmetic practices are primarily type A. The FDA has approved three separate BoNT-A formulations for cosmetic purposes: onabotulinum toxin A (BoNT-ona), incobotulinum toxin A (BoNT-inco), and abobotulinum toxin A (BoNT-abo). BoNT-ona was the first type to be approved by the FDA for cosmetic indications and is the subject of a large proportion of the botulinum research. Each BoNT formulation contains the 150kDA neurotoxin protein, plus varying amounts of non-toxin associated proteins. BoNT-inco is 150kD and free from complexing proteins, where as BoNT-ona and BoNT-abo are complexed with non-toxin proteins and are 900kD and 500kD respectively (Carruthers and Carruthers, 2008; Bonaparte et al., 2013; Schantz and Johnson, 1992).

In addition to different toxin associated proteins, formulations vary in their potency. Formulations of BoNT-abo are thought to be equivalent to BoNT-inco. BoNT-ona's potency, however, is thought to be 1:2–1:3 relative to BoNT-abo's (Carruthers and Carruthers, 2008). Although no clear conversion ratio has been established, as per a consensus review by Carruthers et al., a dose ratio of 1:2.5 can be assumed (Carruthers et al., 2013b).

In terms of clinical efficacy, studies of BoNT-ona and BoNT-inco have found them comparable in the treatment of glabellar lines and crow's feet with similar time to onset, duration, and side effect profiles (Sattler et al., 2010; Prager et al., 2010). Studies comparing efficacy of BoNT-ona and BoNT-abo at a conversion factor of 1:2.5 in the treatment of palmar hyperhidrosis also found no statistically significant difference in onset, duration, or effect (El Kahky et al., 2013).

Ultimately, the selection of the type of BoNT is clinician and patient preference dependent. At this time, there is insufficient evidence to comment on superiority (Frevert, 2015b). In this review, however, dosages will be based on BoNT-ona as this is the oldest and most studied formulation.



4. Use of botulinum for cosmetic purposes

Prior to injecting BoNT, the practitioner must examine the positions and movements of the patient's facial muscles both when active and at rest. Facial musculature is inherently asymmetric and planning for BoNT injections must compensate for this. Signs of unequal muscle strength can be gleaned from greater dynamic movements, deeper furrows, and discrepancies in apparent muscle mass. These features should be accounted for and discussed with the patient prior to any type of injection.

5. Upper face

5.1. Glabellar lines

Treatment of the glabellar lines with BoNT was the first of two cosmetic uses of BoNT approved by the FDA. The treatment of glabellar lines using BoNT is by far the most common cosmetic application of the toxin (Dorizas et al., 2014).

The target muscles in the treatment of glabellar lines are the large procerus muscle in the middle and the two bellies of the corrugator supercilii bilaterally. These muscles are responsible for depressing the medial brow. Repetitive contraction of these muscles leads to the glabellar creases. Typically, the contraction of the corrugators is associated with vertical lines and the contraction of the procerus with horizontal lines.

In early dose ranging studies for the use of BoNT in the glabellar region, Carruthers et al. found that increasing the dose of BoNT was associated with increased response and greater efficacy in reducing glabellar rhytides. Dose ranging studies with BoNT-ona found that the optimal initial dose for men was approximately 40 units and 20 units total for women (Carruthers et al., 2005). The toxin is typically injected at three to five separate points including the procerus centrally and 1–2 injections into the corrugators bilaterally, depending on the patient's musculature (Carruthers et al., 2005). The most promising results have been seen in patients with shallow wrinkles only visible with contraction or in patients with shallow folds that can be spread with the fingers (Pribitkin et al., 1997).

In a systematic review of BoNT formulations used in aesthetic dermatology, the most common complications with glabellar injections were bruising and headache (Cavallini et al., 2014). Ptosis of the eyelids, however, is the most concerning complication associated with the treatment of the glabella, occurring when the toxin diffuses across the orbital septum and affects the levator palpebrae superioris. Injecting into the corrugators at least 1 cm above the supraorbital ridge helps to prevent this complication, as does keeping the injection medial to the mid-pupillary line (Klein, 2004). After the procedure, patients may be instructed to remain vertical for three hours, again to limit undesirable diffusion (Carruthers and Carruthers, 1996).

Treatment of ptosis secondary to glabellar injections includes use of alpha-adrenergic agonist eye-drops to the affected side, which cause contraction of the adrenergic responsive Müllers muscle, situated below the levator palpebrae superioris muscle. The treatment will cause an elevation of 1–2 mm of the lash margin. Patients usually require drops several times daily until the ptosis resolves.