

Invited Review Paper Cosmetic Surgery

The use of botulinum toxin type A in cosmetic facial procedures

G. W. C. Jaspers, J. Pijpe, J. Jansma

Department of Oral and Maxillofacial Surgery,
University Medical Center Groningen,
Groningen, The Netherlands

G. W. C. Jaspers, J. Pijpe, J. Jansma: The use of botulinum toxin type A in cosmetic facial procedures. Int. J. Oral Maxillofac. Surg. 2011; 40: 127–133. © 2010 International Association of Oral and Maxillofacial Surgeons. Published by Elsevier Ltd. All rights reserved.

Abstract. Over the past decade, facial cosmetic procedures have become more commonplace in dentistry and oral and maxillofacial surgery. An increasing number of patients seek minimal invasive procedures. One of the most requested procedures is treatment with botulinum toxin type A (BoNTA). Treatment of dynamic rhytids and lines with BoNTA is effective and produces high rates of improvement with rapid onset and long duration of action (longer than 4 months for some patients) compared with placebo. This paper considers the history and pharmacology of this neurotoxin, and focusses on the literature concerning the treatment of different facial areas with BoNTA. It also presents clinical guidelines on the treatment of glabellar lines, the frontalis muscle, peri-orbital lines, gummy smile and masseter muscle hypertrophy. Knowledge about the mechanisms of action and the ability to use BoNTA as an adjunctive treatment are mandatory for those working in the field of cosmetic facial surgery.

Keywords: Botulinum toxin; Facial aesthetics; Cosmetic facial surgery; Injectables.

Accepted for publication 17 September 2010
Available online 20 October 2010

Invasive and non-invasive facial cosmetic procedures are becoming commonplace in oral and maxillofacial surgery. Apart from invasive surgical procedures, many patients choose rejuvenation with injectables such as botulinum toxin type A (BoNTA). In the USA, from 2000 to 2008, minimally invasive cosmetic treatment with BoNTA increased by 537% to 5 million treatments a year, while surgical cosmetic procedures such as blepharoplasty and facelift decreased by 16–32% to 220,000 and 113,000 procedures, respectively². With aging, changes become apparent through the face. Following loss of volume and elasticity in the facial skin, tissues follow gravity in a downward movement. This leads to the formation of wrinkles and fine lines around the eyes and mouth. This is due

to hyperdynamic contraction of the underlying muscles in these areas. When a muscle contracts, the overlying skin folds perpendicular to the direction of the muscle²⁹. This creates a dynamic wrinkle that can be treated with BoNTA. When age advances, the jaw line begins to sag and more static wrinkles form due to underlying fat displacement and long term skin folding. Factors that are responsible for facial aging include soft tissue maturation, muscular facial activity, smoking habits and solar changes²⁹. Botulinum toxin has shown impressive results in softening dynamic wrinkles and can be used as a treatment of first choice or as a ‘test drive’ for a more permanent surgical procedure. There is little scientific data about the effects of BoNTA in the cosmetic field regarding dose-ranging, effectiveness, fol-

low up and patient selection⁴. A recent review found 11 randomized controlled clinical trials on the use of BoNTA in facial aesthetics¹⁹. Apart from the mechanisms of action of BoNTA, contraindications and restrictions, this article will focus on the most frequent cosmetic indications in the upper facial area (glabella, frontal area and peri-orbital lines) and on gummy smile treatment and masseter hypertrophy. When treating patients with BoNTA, the facial expression can be softened and rejuvenated in dynamic, and to a lesser extent, in static dimensions.

Historical perspective

Food-borne botulism has been around as long as man has tried to preserve and store food. There is little documentation from

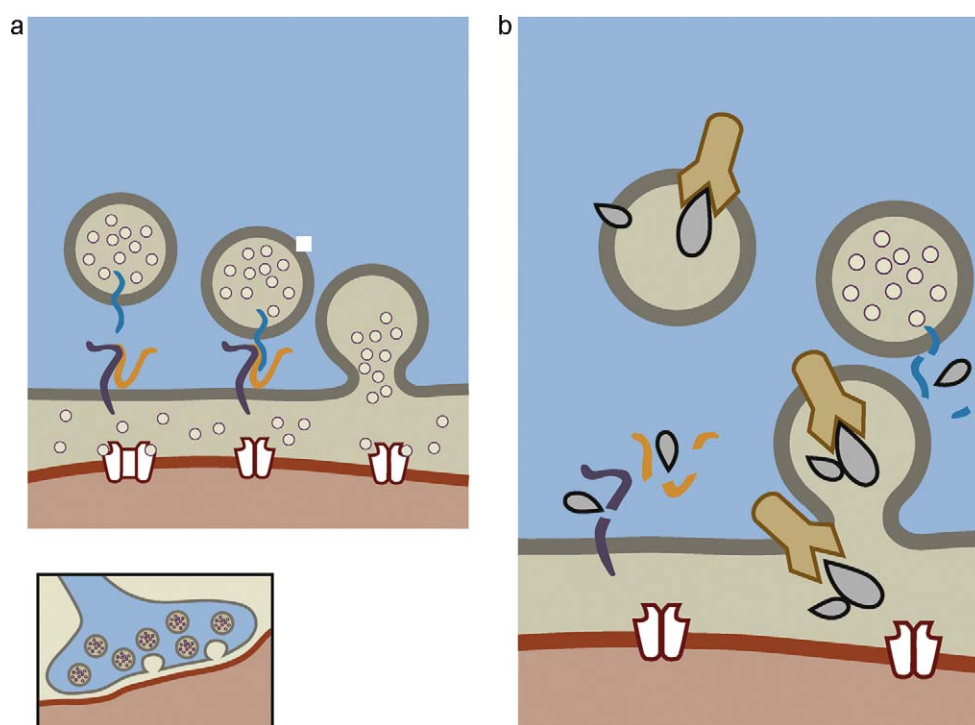


Fig. 1. (a) Lower figure depicts normal nerve ending to muscle endplate function. Upper figure depicts acetylcholine fusing with the nerve ending membrane and crossing the membrane leading to contraction. (b) BoNTA binding to nerve ending. It inhibits the discharge of acetylcholine into the synapse by bonding to the nerve at the neuromuscular ending.

before the late 18th century, when romantic poet and medical officer Justinus Kerner described a case of lethal food poisoning. He described symptoms of mydriasis, diplopia, gastrointestinal complaints and progressive muscle paralysis after consumption of meat and blood sausage. This is also the derivation of the name botulism (*botulus* is sausage in Latin)^{16,17}. It was not until 1897 that the Belgian microbiologist Emile van Ermenegem isolated the bacillus *Botulinum* while investigating an outbreak of botulism. The pathogen was later renamed as a neurotoxin-producing Gram-positive bacterium *Clostridium botulinum*²⁷. Research into the potential use of the botulinum toxin as a biological weapon was intensified during both world wars. After World War II, botulinum toxin was used in local injections to reduce the activity of hyperactive muscles. The American ophthalmologist, Scott, successfully used BoNTA in blepharospasm and strabismus¹⁹. This led to the first approval by the US Food and Drug Administration (FDA) as 'Oculinum' in 1989. The Allergan (Irvine, USA) company received FDA approval to change the therapeutic name from Oculinum to Botox®. In the same period, Ipsen (Slough, UK) developed and received approval for production of Dysport® for the European market⁸.

History of the cosmetic use of BoNTA

In 1990, the dermatologist, JEAN CARRUTHERS, and ophthalmologist, ALASTAIR CARRUTHERS, published their first report on the cosmetic use of BoNTA. They discovered this new indication by serendipity while treating patients for blepharospasm, and saw cosmetic side-effects as dynamic rhytids subsequently disappeared. This was the start of their substantial research on the cosmetic use of BoNTA, which led to several publications^{8,11}. Several other authors recognized the potential of BoNTA for the treatment of hyperkinetic lines on the face, which lead to widespread acceptance of the technique after 1995^{4,6,23}. Since 2009, BoNTA has been formally registered in several European countries for cosmetic use in the glabella region; use in all other regions remains an off-label use of this product.

Pharmacology

Voluntary muscle contraction is a response to stimulation by action potentials passing along a nerve to the muscle end plate. Once the action potentials reach a synapse at the neuromuscular junction, they stimulate an influx of calcium into the cytoplasm of the nerve ending, and mobilization of acetylcholine towards the

synapse occurs. Acetylcholine fuses with the nerve ending membrane and then crosses the synapse to bind with receptors on the muscle fibre, which leads to contraction (Fig. 1a). BoNTA inhibits the discharge of acetylcholine into the synapse by bonding to the nerve at the neuromuscular ending. The toxin is then internalized via receptor-mediated endocytosis, and a toxin-containing vesicle is formed within the nerve ending. These internalized vesicles inhibit the acetylcholine protein (Synaptosomal Associated Protein-25) that is located on the cell membrane (Fig. 1b). This inhibits muscle contraction, which leads to reversible muscle atrophy²¹. The first cessation of muscle function occurs after 2–3 days, and the maximum effect occurs after 2 weeks. Binding of BoNTA to the nerve is irreversible, and recovery of muscle function occurs by proliferation of axonal nerve buds to the target muscle and regeneration of muscle end plates. Clinically relevant reduction of muscle contraction last for 4 months in glabellar lines and can last up to 6 months in the frontalis region, depending on individual variation^{9,13,14,29}.

Dosage and administration

Several companies manufacture BoNTA. Vistabel® (also known as Botox®, Aller-

gan, Irvine, USA) and Azzalure® (Ipsen, Slough, UK) have recently been registered for facial cosmetic use in Europe. The dosages mentioned in this article are based on Vistabel®, which is delivered in a 50 IU vial (or a 100 IU vial). The contents of the 50 IU vial are diluted in 1.25 ml 0.9% saline solution to give a solution of 4 IU/0.1 ml. Using this concentration, small amounts of solution can be injected, giving a precise placement of toxin and less diffusion. When using a less potent solution, the amount of injected solution increases, and diffusion into neighbouring muscles can increase. This can cause unwanted side-effects such as blepharoptosis^{14,15}.

Reconstitution of the botulinum toxin takes place by gently injecting the diluent into the vial, avoiding the formation of foam in the complex, which may result in toxin denaturation²¹. Once reconstituted, the drug must be stored at a temperature of 2–8 °C. After reconstitution, the drug should be used within 4–8 h, as recommended by the manufacturer. This recommendation is for sterility and efficacy purposes. Recent studies have shown that toxin efficacy remains the same until 15 days after reconstitution, and bacterial contamination does not take place²⁰.

The most commonly used syringes are 1 ml insulin syringes with removable 30 gauge needles. These needles are not traumatic to tissue and minimally painful because of their size. Local anaesthesia is usually not necessary. There is still debate on skin preparation before injection. There is no evidence-based consensus on whether skin should be disinfected with alcohol or chlorhexidine to prevent local infection, or that this should be avoided because of the belief that alcohol can inactivate the BoNTA¹⁹.

Contraindications

Administration of BoNTA should be avoided during pregnancy and breast feeding and in patients with disorders of the neuromuscular junction (such as myasthenia gravis, Lambert-Eaton syndrome) and neurodegenerative diseases such as amyotrophic lateral sclerosis. Simultaneous use of aminoglycoside antibiotics (gentamycin, tobramycin) should be avoided because of their potentiating effect on BoNTA. Other theoretical drug interactions could occur with calcium channel blockers, cyclosporine and cholinesterase inhibitors. Highly frequent administration of BoNTA (more than every 12 weeks) and repeated exposure can lead to formation of neutralizing antibodies against the toxin which lead to disappointing results⁷.

Safety of BoNTA in cosmetic procedures and adverse events

Pharmacological BoNTA has an excellent safety record that is diametrically opposed to the devastating presentation of systemic botulism secondary to food poisoning. The estimated lethal dose of BoNTA for humans falls in the range of 2500–3000 U²⁵.

The most common patient complaints about BoNTA are injection site pain and bruising. During clinical trials of BoNTA for glabellar lines and horizontal forehead rhytids, the most frequently reported adverse events were headache, asymmetric appearance, lack of facial animation and blepharoptosis. In patients with pre-existing lower lid laxity, weakening of the orbicularis oculi muscle with BoNTA can cause ectropion²⁸.

Indications

As with any other type of treatment, before performing cosmetic procedures with BoNTA, both patient and physician should discuss treatment expectations, to prevent

disappointment. Consistent with current treatment approaches that aim to provide a more natural and relaxed look, clinical practice frequently involves treating multiple facial areas rather than a single area. Research has indicated that this is consistent with better patient-reported outcomes¹⁰. BoNTA reduces the mimetic effects of wrinkles and folds, and should therefore be applied in areas of dynamic motion, such as the glabella, frontal region, and peri-orbital lines. Static wrinkles and very deep folds are less suitable for the use of BoNTA alone, and a combination with other injectables, such as hyaluronic acid is preferred. The safest indications are dynamic wrinkles in the upper third of the face. The existence of rhytids in this area is based on the equilibrium of opposing elevator and depressor muscles, which are outlined in Fig. 2^{10,29}. More advanced indications are the perioral area, which is mostly combined with hyaluronic acids, and the gummy smile. All injection sites and advised injection units are outlined in Table 1. There are differences in the dosage relating to muscle volume in males and females. In gen-

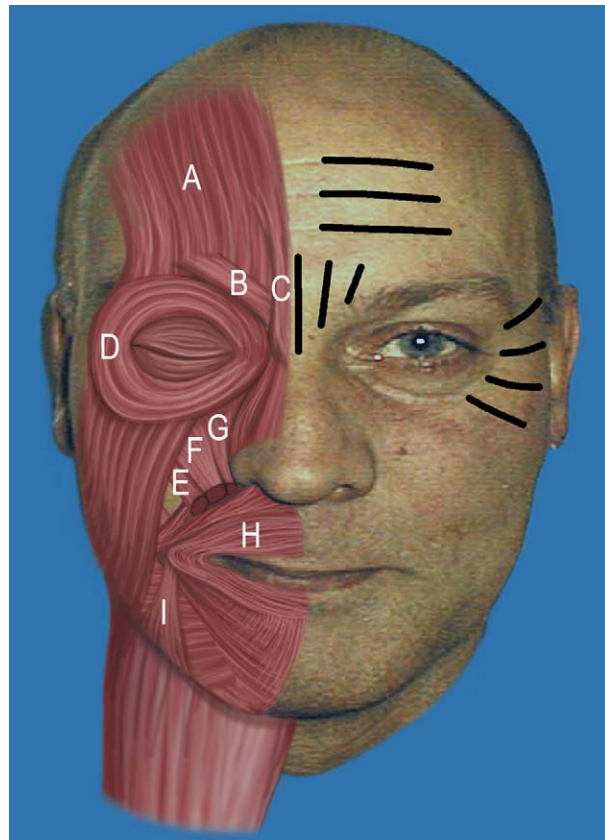


Fig. 2. Left: skin with accentuated horizontal forehead rhytids, glabellar rhytids and crow's feet. Right: normal muscle anatomy with: a, Frontalis; b, Corrugator supercilii; c, Procerus; d, Orbicularis oculi; e, Zygomatic minor; f, Levator labii superioris; g, Levator labii superioris alaeque nasi; h, Orbicularis oris; and i, Depressor anguli oris.

Table 1. Facial indications and advised injection units with BoNTA 100 IU diluted in 2.5 ml 0.9% saline solution, which gives a solution of 4 IU/0.1 ml.

Indication	Number of injection sites	IU per injection site	Total IU injected	MI solution per injection site
Glabella	5	4	20	0.1
Frontalis	5–7	4	20–28	0.1
Crow's feet	2 × 3	4	24	0.1
Gummy smile	2	4	8	0.1
Masseter hypertrophy	2 × 3	12	72	0.3

eral, males have a larger muscle volume and require more units of BoNTA to achieve the same results as female patients^{9,13,14}.

Glabella region

Treating glabellar lines with BoNTA is successful and predictable. The lines are formed by the continuous action of the procerus and corrugator supercilii muscles. At first the wrinkles appear only to be dynamic, but as age progresses static folds form. Excellent results are achieved when injecting these lines with BoNTA. Patients are asked to frown before injection while the largest muscle body of the procerus and corrugator muscles is palpated (Fig. 3a). The corrugator supercilii muscle is injected 1 cm above the orbital rim. With a distance less than 1 cm diffusion of the material into the medial part of

the eyebrow is possible and may lead to local eyebrow ptosis. This effect is temporary and not treatable¹⁰. Female patients require 5×4 U (0.1 ml)¹⁴; most males require up to 5×6 U (0.15 ml) depending on muscle tone⁹. In a period of up to 2 weeks, the glabellar lines will clear out (Fig. 3b).

Frontalis muscle

The large frontalis muscle is the only elevator muscle in the upper face. It originates superiorly to the eyebrow at the galea apo-neurotica and is responsible for producing horizontal forehead rhytids. Complete paralysis of this muscle causes unwanted eyebrow ptosis, and should be avoided. Leaving mobility in the areas above the eyebrow maintains normal projection of the eyebrow and some mimic motion. The injection sites should be

extended far enough towards the lateral to avoid the lateral part of the eyebrow being pulled up excessively. This results in an unnatural look, also described as 'mephisto'¹⁸. The correct procedure is to choose five or seven injection sites with a triangular distribution and at a position no lower than half way between the hairline and the eyebrow (Fig. 4a). Doses of 7×4 U (0.1 ml) have been shown to be equally effective as higher (48 U) doses. Lower doses (16 U) show an almost equal response rate, but faster relapse¹². An injection site within 2 cm of the most lateral extension of the eyebrow should be chosen as the most lateral injection point (Fig. 4b).

Peri-orbital lines

Peri-orbital lines and wrinkles are produced by contraction of the lateral aspect

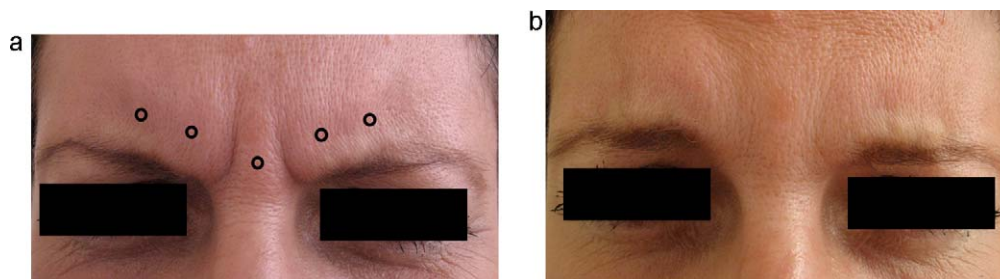


Fig. 3. (a) Clear view of the largest muscle body of the procerus and corrugator muscles, when patient frowns. Choose one injection point in each muscle belly, each receiving 0.1 ml of solution (4 IU). See Table 1 for injection details. (b) Two weeks after injection with BoNTA. Patient asked to frown. Adequate pareses of procerus and corrugator muscles, without medial blepharoptosis.

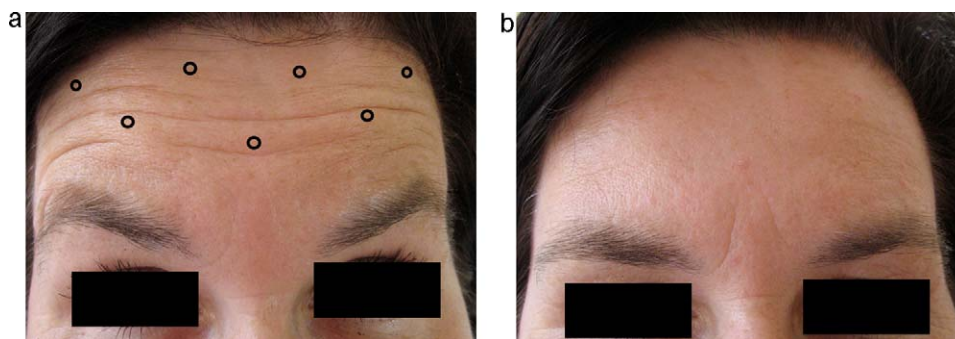


Fig. 4. (a) Frontalis muscle in action with preferred injection sites. Adequate distance from the eyebrow is chosen to avoid brow ptosis. In this patient, seven injection points were used because of far lateral extension of the frontalis muscle. (b) Two weeks after injection with BoNTA in an attempt to raise eyebrows. Minimal lowering of lateral brow, and sufficient pareses of the frontalis muscle.

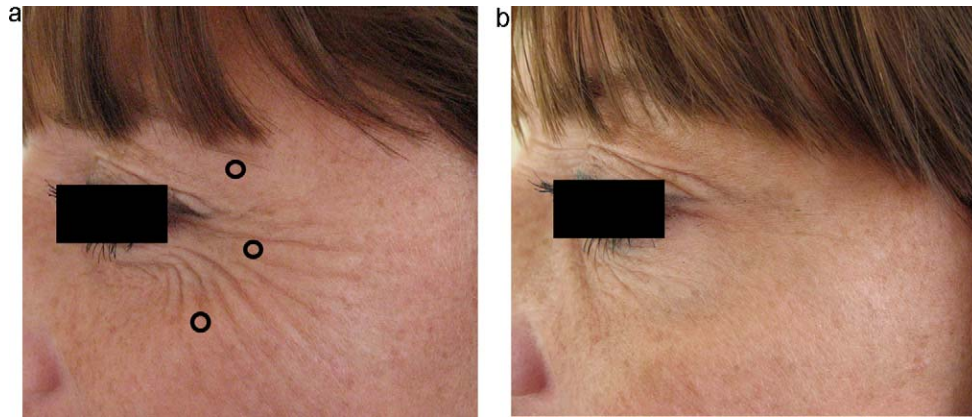


Fig. 5. (a) Peri-orbital lines appear when patient is asked to smile. Three injection points are chosen with an equal distribution following the outer rim of the orbit. Distance to lateral orbital rim should be 1 cm. The upper injection point is just below the eyebrow for lateral lifting effect on the eyebrow. (b) Two weeks after injection with BoNTA. Slight elevation of the lateral eyebrow, and clear reduction of peri-orbital lines when broad laugh is asked for.

of the orbicularis oculi muscle. The superficial spread of the muscle gives the typical crow's feet appearance to the skin when smiling. These lines begin to appear at around 20–25 years of age. At first they appear only as a dynamic wrinkle, but they evolve into a static wrinkle and are also present at rest. There is a trend for greater treatment response rates for younger subjects (<50 years) than older subjects (>50 years) 4 weeks after injection. Changes in the elasticity of the skin with aging may contribute to this observation, because the benefits of treatment with BoNTA may be less apparent if the skin is lax³. Three injection sites lateral to each eye are almost always sufficient to give relaxation to the part of the orbicularis oculi muscle that is responsible for crow's feet (*Fig. 5a*). Each injection site receives 4 U (0.1 ml). This gives adequate response rates up to 16 weeks post-injection^{3,22}. When treating these lines, it is important

to start with palpation of the lateral orbital rim, and plan the medial injection site 1 cm lateral to it. This prevents diffusion into the orbit, and into the orbital muscles¹⁵. By choosing the upper injection site just below the eyebrow, an aesthetically pleasing lift of the lateral eyebrow can be achieved as a beneficial extra effect of this treatment. The caudal injection site is 1–2 cm below the medial one, and stays away from the orbital rim for the same reason (*Fig. 5b*).

Gummy smile

Patients with high to excessive gingival display during smiling (gummy smile) and pronounced tooth show at rest can be treated with a combined orthodontic/orthognathic treatment with a surgical maxillary intrusion. This not only provides a definitive solution to excessive gingival display in cases of vertical max-

illary excess, but also requires a relatively large investment from the patient. A gummy smile produced by hyperfunctional upper lip elevating muscles is usually less satisfyingly solved by maxillary surgery. It is often a transitory problem that diminishes with advancing age, as muscles lose their initial hypertone. In this patient category satisfactory results can be achieved with BoNTA injections. Vertical movement of the upper lip is produced by the levator labii superioris alaeque nasi muscle, the levator labii superioris muscle, and to a lesser extent by the zygomaticus minor muscle. Injection sites are determined by muscle animation (smiling) and palpation to ensure the precise muscle location²⁶. Special care must be taken to ensure this exact location, as an asymmetric smile and inability to pucker have been described due to misplacement of BoNTA²⁴. The injection site is determined lateral to each nostril, where 4 U

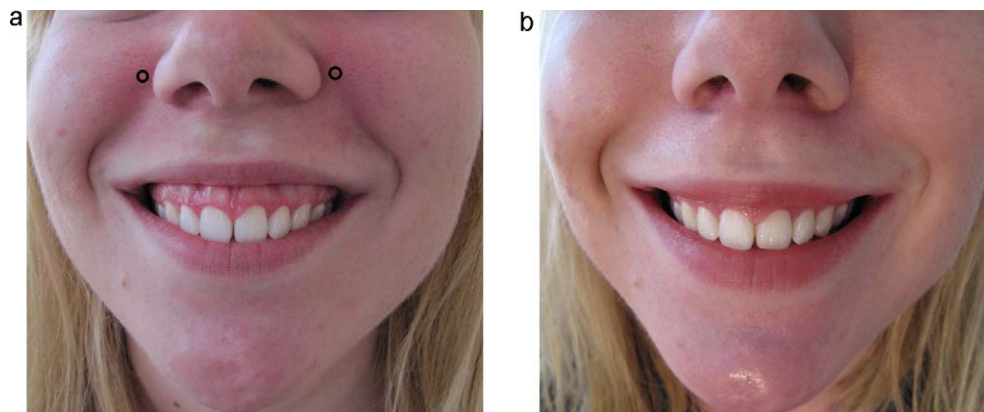


Fig. 6. (a) Clear gummy smile appearance after orthodontic regulation. After meticulous palpation of levator labii superioris alaeque nasi muscle during muscle animation (smiling and active upper lip retraction) one injection site at each side of the nostril is chosen (4 IU). (b) Reduction of gummy smile appearance in full smile two weeks after injection with BoNTA. Notice paranasal relaxation and natural appearance of the upper lip.

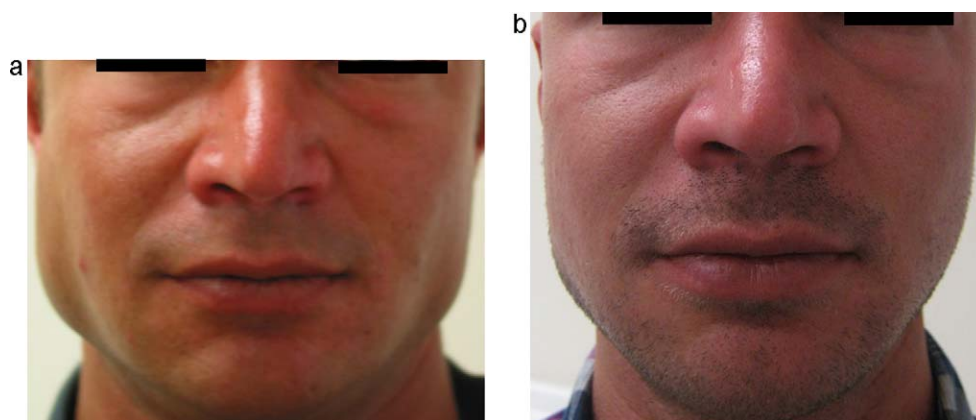


Fig. 7. (a) Bilateral swelling in the mandibular angle region due to masseteric muscle hypertrophy. (b) Reduction of hypertrophic masseteric muscle appearance 4 weeks after injection with BoNTA.

(0.1 ml) is injected (Fig. 6a). This gives a vertical relaxation of the upper lip but maintains the ability to smile and pout the lips (Fig. 6b). Relaxation will gradually relapse, and retreatment will be necessary after approximately 6 months.

Masseter hypertrophy

Masseteric muscle hypertrophy may present as a bilateral painless swelling in the region of the angle of the mandible (Fig. 7a). The aetiology is unexplained in most cases. It has been attributed to malocclusion, bruxism, and clenching. Intramuscular injection with BoNTA leads to reduction of the thickness of the masseter, without serious side-effects. Randomized clinical trials on this subject are not available¹. Before treatment with BoNTA, treatment for parafunctional bruxism or clenching with splint therapy should be carried out¹. Injection sites are identified by palpation of the muscle during clenching. BoNTA is administered percutaneously at three points in the thickest part of the hypertrophic muscle at the inferior mandibular border. Each injection site receives 12 U (0.3 ml). This large amount of injected BoNTA will diffuse through the muscle, which makes more injection sites unnecessary. After recurrence, additional injections with BoNTA can be effective (Fig. 7b).

Discussion

The use of BoNTA in cosmetic facial procedures is a reliable way to enhance aesthetics in the upper and lower face. The use of BoNTA in non-surgical facial cosmetic procedures produces high rates of improvement with rapid onset and long duration of action (longer than 4 months

for some patients) when compared with placebo¹⁹. The indications described are highly effective and the incidence of adverse effects associated with BoNTA is similar to those with placebo, with the exception of blepharoptosis, which is reported to occur in 0–5.4% of cases after treatment of glabellar lines, and injection-related headache during the first day¹⁹. Working with a neurotoxin with the potency of BoNTA requires sufficient knowledge of pharmacology and dosing in different treatment areas. After mastering the most common indications for BoNTA in the face, one can also treat more difficult areas such as the peri-oral region^{5,26}.

Maxillofacial surgeons have a good understanding of facial anatomy and see patients with aesthetic demands in the peri-oral and facial region frequently. The ability to use BoNTA as an adjunctive treatment is necessary when working in the field of cosmetic facial surgery.

Funding

None.

Competing interests

None declared.

Ethical approval

Not required.

References

1. AL-MUHARRAQI MA, FEDOROWICZ Z, AL BAREEQ J, NASSER M. Botulinum toxin for masseter hypertrophy. *Cochrane Database Syst Rev* 2009: CD007510.
2. AMERICAN SOCIETY OF PLASTIC SURGEONS. 2009 report of the 2008 Statistic National Clearinghouse of Plastic Surgery Statistics. 2010.
3. ASCHER B, RZANY BJ, GROVER R. Efficacy and safety of botulinum toxin type A in the treatment of lateral crow's feet: doubleblind, placebo-controlled, dose-ranging study. *Dermatol Surg* 2009; **35**: 1478–1486.
4. BENEDETTO AV. The cosmetic uses of Botulinum toxin type A. *Int J Dermatol* 1999; **38**: 641–655.
5. BLITZER A, BINDER WJ, AVIV JE, KEEN MS, BRIN MF. The management of hyperfunctional facial lines with botulinum toxin. A collaborative study of 210 injection sites in 162 patients. *Arch Otolaryngol Head Neck Surg* 1997; **123**: 389–392.
6. BLITZER A, BRIN MF, KEEN MS, AVIV JE. Botulinum toxin for the treatment of hyperfunctional lines of the face. *Arch Otolaryngol Head Neck Surg* 1993; **119**: 1018–1022.
7. BORODIC G. Immunologic resistance after repeated botulinum toxin type a injections for facial rhytides. *Ophthal Plast Reconstr Surg* 2006; **22**: 239–240.
8. CARRUTHERS J, CARRUTHERS A. Treatment of glabellar frown lines with C. botulinum-A exotoxin. *J Dermatol Surg Oncol* 1992; **18**: 17–21.
9. CARRUTHERS A, CARRUTHERS J. Prospective, double-blind, randomized, parallel-group, dose-ranging study of botulinum toxin type A in men with glabellar rhytids. *Dermatol Surg* 2005; **31**: 1297–1303.
10. CARRUTHERS A, CARRUTHERS J. Eyebrow height after botulinum toxin type A to the glabella. *Dermatol Surg* 2007; **3**: S26–S31.
11. CARRUTHERS A, CARRUTHERS J. History of the cosmetic use of Botulinum A exotoxin. *Dermatol Surg* 1998; **24**: 1168–1170.
12. CARRUTHERS A, CARRUTHERS J, COHEN J. A prospective, double-blind, randomized, parallel-group, dose-ranging study of botulinum toxin type a in female sub-

- jects with horizontal forehead rhytides. *Dermatol Surg* 2003; **29**: 461–467.
13. CARRUTHERS A, CARRUTHERS J, FLYNN TC, LEONG MS. Dose-finding, safety, and tolerability study of botulinum toxin type B for the treatment of hyperfunctional glabellar lines. *Dermatol Surg* 2007; **33**: S60–S68.
 14. CARRUTHERS A, CARRUTHERS J, SAID S. Dose-ranging study of botulinum toxin type A in the treatment of glabellar rhytids in females. *Dermatol Surg* 2005; **31**: 414–422.
 15. CORONEO MT, ROSENBERG ML, CHEUNG LM. Ocular effects of cosmetic products and procedures. *Ocul Surf* 2006; **4**: 94–102.
 16. ERBGUTH FJ. Historical notes on botulism, *Clostridium botulinum*, botulinum toxin, and the idea of the therapeutic use of the toxin. *Mov Disord* 2004; **19**(Suppl 8):S2–S6.
 17. ERBGUTH FJ. From poison to remedy: the chequered history of botulinum toxin. *J Neural Transm* 2008; **115**: 559–565.
 18. FAGIEN S, CARRUTHERS JD. A comprehensive review of patient-reported satisfaction with botulinum toxin type a for aesthetic procedures. *Plast Reconstr Surg* 2008; **122**: 1915–1925.
 19. GADHIA K, WALMSLEY AD. Facial aesthetics: is botulinum toxin treatment effective and safe? A systematic review of randomized controlled trials. *Br Dent J* 2009; **207**: 1–9.
 20. HEXSEL D, RUTOWITSCH MS, DE CASTRO LC, DO PRADO DZ, LIMA MM. Blind multicenter study of the efficacy and safety of injections of a commercial preparation of botulinum toxin type A reconstituted up to 15 days before injection. *Dermatol Surg* 2009; **35**: 933–939.
 21. KLEIN AW. Dilution and storage of botulinum toxin. *Dermatol Surg* 1998; **24**: 1179–1180.
 22. LOWE NJ, ASCHER B, HECKMANN M, KUMAR C, FRACZEK S, EADIE N. Double-blind, randomized, placebo-controlled, dose-response study of the safety and efficacy of botulinum toxin type A in subjects with crow's feet. *Dermatol Surg* 2005; **31**: 257–262.
 23. LOWE NJ, MAXWELL A, HARPER H. Botulinum A exotoxin for glabellar folds: a double-blind, placebo-controlled study with an electromyographic injection technique. *J Am Acad Dermatol* 1996; **35**: 569–572.
 24. NIAMTU III J. Botox injections for gummy smiles. *Am J Orthod Dentofacial Orthop* 2008; **133**: 782–783.
 25. PENA MA, ALAM M, YOO SS. Complications with the use of botulinum toxin type A for cosmetic applications and hyperhidrosis. *Semin Cutan Med Surg* 2007; **26**: 29–33.
 26. POLO M. Botulinum toxin type A (Botox) for the neuromuscular correction of excessive gingival display on smiling (gummy smile). *Am J Orthod Dentofacial Orthop* 2008; **133**: 195–203.
 27. TING PT, FREIMAN A. The story of *Clostridium botulinum*: from food poisoning to Botox. *Clin Med* 2004; **4**: 258–261.
 28. WOLLINA U, KONRAD H. Managing adverse events associated with botulinum toxin type A: a focus on cosmetic procedures. *Am J Clin Dermatol* 2005; **6**: 141–150.
 29. ZIMBLER MS, KOKOSKA MS, THOMAS JR. Anatomy and pathophysiology of facial aging. *Facial Plast Surg Clin North Am* 2001; **9**: 179–187.

Address:
 G.W.C. Jaspers
 Department of Oral and Maxillofacial
 Surgery
 University Medical Center Groningen
 P.O. Box 30001
 9700 RB
 Groningen
 The Netherlands
 Tel: +31 50 3613840
 Fax: +31 50 3612831
 E-mail: g.w.c.jaspers@kchir.umcg.nl