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EXPERT OPINION

Consensus Statement on the Use of Botulinum Neurotoxin in the Middle East

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Background: Aesthetic minimally invasive procedures have become very popular and culturally acceptable among Middle Eastern populations. Botulinum neurotoxin type A (BoNTA) is a valuable treatment modality for many cosmetic as well as therapeutic indications. The presence of BoNTA in our toolkit has revolutionized the field of aesthetic medicine to the point where it is now one of the most commonly performed cosmetic procedures worldwide. This consensus considers popular on- and off-label BoNTA indications in the Middle East.

Methods: A multinational group of ten key opinion leaders, experts in facial plastic surgery and dermatology, convened the Middle East Aesthetics Consensus Group and reviewed the aesthetic applications of BoNTA. Recommendations and position statements were drafted based on the integration of the panel's clinical experience with published data, targeted to the practices implemented in the Middle Eastern and the global population.

Results: Guidance statements are presented covering Middle Eastern facial characteristics and beauty ideals, BoNTA characteristics, pre-operative counselling, treatment indications and anatomical considerations, off-label and special uses including high-dose recommendations, and post-treatment advice. Throughout, an evidence-based approach to selection of products and injection techniques is provided, supplemented by the experts' advice on injections dosages and placement.

Conclusion: This consensus reflects the knowledge and expertise of physicians practicing in the Middle East. The panel acknowledged the use of on-label indications and variability in the toxin formulations and immunogenicity and agreed upon a wide use of "off-label" indications.

Keywords: aesthetic use, botulinum neurotoxin type A, consensus, Middle East

Introduction

Botulinum neurotoxin type A (BoNTA) injections have gained significant popularity in the field of aesthetics due to their well-tolerated safety profile, complete reversibility, and aesthetic benefits. As a result, the on- and off-label uses of BoNTA have increased worldwide, including in the Middle East.[1]

The Middle East is a culturally diverse region with various ethnic groups who have structural differences in facial anatomy and anthropometry when compared to Western populations, on which most aesthetic procedure information is based. Although non-invasive aesthetic treatments are widely accepted and popular in the region,[2,3] the lack of published data on Middle Eastern ethnic anthropometry and beauty preferences has made it challenging to develop effective facial treatment strategies that consider ethnic aesthetic deficiencies and facial proportions. While clinical practice guidelines

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for BoNTA use in Eastern European,[4] Asian,[5] and global populations[6] have been established, published data focusing on the Middle East as a whole are limited to individual ethnic groups.[3,7–9]

The purpose of this publication was to provide practical consensus recommendations for the optimal use of BoNTA in individuals of Middle Eastern ethnicity, considering the underlying facial anatomy and treatment preferences of those seeking aesthetic rejuvenation.

Consensus Objectives and Methodology

On May 30, 2022, a multinational group of ten key opinion leaders, experts in facial plastic surgery and dermatology with extensive experience of BoNTA injections in a range of ethnic groups, convened the Middle East Aesthetics Consensus Group. The objectives of the meeting were to review aesthetic applications of BoNTA and create recommendations and position statements for its use in subjects with Middle Eastern ethnicity, based on the integration of the panel's clinical experience with published data.

A series of questionnaires addressing all aspects of BoNTA treatment were distributed to experts before the meeting and served as the basis for knowledge regarding medical management and subsequent discussions (Supplementary Figure 1). The meeting followed a structured consensus approach conducted by an experienced moderator.

The panelists considered that:

1. There was an unmet need for an expert review of the existing evidence as it relates to individuals of Middle Eastern descent, to help guide practitioners to achieve safe as well as optimal outcomes for their patients.
2. The current consensus is intended as an aid to practitioners' own experience and should be tailored to individual patients and regional variations. It is not intended to be a substitute for extensive training and mentorship in this field.

The consensus process included one round of voting after discussion and consensus was defined as achievement of ≥75% agreement for each statement. When consensus was not reached, or clarification of a recommendation statement was requested, members of the expert panel discussed whether the statement should be amended or deleted.

This publication presents the panel's recommendations and position statements for BoNTA, based on integration of experts' clinical experience with published data.

Results

Middle Eastern Facial Characteristics and Beauty Ideals

Facial measurements obtained from anthropometric studies reveal that there are remarkable differences between various ethnic groups, including Middle Eastern populations. Middle Eastern individuals tend to have heavier faces, which may result in mid-face sagging with age leading to lower third jowling.[3] Individuals of Middle Eastern descent have a range of Fitzpatrick skin types, from III to VI, and are less likely to suffer premature fine lines and wrinkles from sun damage and generally have thicker skin than their Caucasian counterparts.

Data from a survey of 17 practicing dermatologists and plastic surgeons from across the Middle East have defined which facial features are considered attractive and sought after by Middle Eastern women.[3] While there was some variation between countries, aesthetic ideals across the region were for oval or round faces; temple fullness; pronounced, elevated, and arched eyebrows; large almond-shaped eyes; well-defined and laterally full cheeks; a small and straight nose; full lips; a well-defined jawline; and a prominent, pointed chin. Any interventional procedures performed in individuals of Middle Eastern descent should respect these ethnic preferences. The research also revealed that among those under the age of 40, social media and friends were the most influential factors cited by patients considering cosmetic interventions.

Several experts noted that in Middle Eastern countries a large proportion of the population is under the age of 35 years old. Younger age groups are increasingly focused on how they look and the demand for beautification using

minimally invasive aesthetic procedures is rising in both women and men. Overall, the population is regarded as very open to neuromodulator treatment.

Experts noted that each patient is unique in terms of his or her anatomy and facial ratios, so that treatment must be tailored to the individual.

Toxin Characteristics Influencing Selection

AbobotulinumtoxinA, onabotulinumtoxinA, and incobotulinumtoxinA are the three main BoNTA commercial formulations officially registered and widely available across the Middle East. These formulations share a common mechanism of action that involves presynaptic blockade of acetylcholine release, but differ in their manufacturing processes, structure, pharmacological properties and stabilizing excipients. As a result, there are differences in potency and immunogenicity, which can affect clinical efficacy and safety.[10] Additional toxins are available in some Middle Eastern countries including prabotulinumtoxinA (Nabota), letibotulinumtoxin (Botulax), and Neuronox, but experience with these preparations is limited and they are not included in this consensus document.

Immunogenicity

The three reference BoNTA formulations differ in their content of non-toxin complexing proteins, incobotulinumtoxinA being the only preparation to contain only the purified core 150 kDa neurotoxin protein. The complexing proteins associated with onabotulinumtoxinA and abobotulinumtoxinA do not play a role in any of the steps involved in blockade of neurotransmitter release, neither are they required for the stability of the toxin complex nor for limiting the spread of the neurotoxin.[11,12] While the complexing proteins have no effect on the treatment response, they have the potential to act as adjuvants and induce a heightened immune response.[13] Other factors that may contribute towards a heightened immune response include: method of administration, with greater trauma potentially resulting in a higher risk of an immunogenic process;[14] cumulative dose of BoNTA over time; frequency of injections; increased indications/dosing, and depth of injections, cutaneous injections are considered to be more immunogenic.[15] Although the incidence of antibody-induced treatment failure is reported to be low for cosmetic applications, the true incidence is difficult to determine. With increasing numbers of individuals receiving BoNTA treatment and expanding indications the number of patients experiencing partial resistance or secondary treatment failure may increase. As a purified neurotoxin, incobotulinumtoxinA has the lowest immunogenic potential of the three formulations.[13,16]

While sharing personal experiences, the panel noted an incidence of partial resistance between 30% and 40% among their practices. They suggested conducting an in-depth survey to accurately determine the reported percentage of partial resistance among aesthetic practices.

Reconstitution

All BoNTA preparations should be reconstituted according to manufacturer's instructions. Clinical experience has shown that the correct reconstitution of a BoNTA formulation is vital for delivering the correct dosage into the target muscle(s). Improper reconstitution may reduce or diminish the effectiveness of the treatment by delivering fewer BoNTA units and jeopardizing the treatment outcome.[17,18] It has been estimated that the typical loss from conventional reconstitution techniques is ±5 U. The size of the needle is also a major factor in product volume/unit loss. Around 0.03 mL of product is lost in the dead space of a 30 G needle; use of needles with no dead space is therefore preferable. Due to the 10% error on the syringe, there is a need to learn how to inject or draw up that amount of volume correctly. Modern syringes with accurate dosing mechanisms that display the number of units for various dilutions can help minimize or completely eliminate solution loss.[10]

Recommendations on Choice of Agent

While there are manufacturer-approved dosages and injection sites for approved BoNTA indications, experts noted that in clinical practice, dosages are variable and should be left to the practitioner's discretion after consideration of a patient's anatomical characteristics and muscle strength.

Experts noted that commercial and social media advertising and promotion can influence choice of BoNTA. The practitioners' expertise, comfort level with use, and pricing of the toxin may also play a role. The expert group agreed:

1. Safety should be the most important feature when choosing a toxin.
2. To reduce the potential risk of treatment failure or secondary non-response, the use of a botulinum toxin A formulation with the lowest protein content should be considered, and minimum dosing intervals respected.
3. Subject to country regulations, BoNTA should be stored in stoppered vials or as aliquots drawn from vials into sterile syringes, for 4 to 6 weeks at 4°C. Freezing after reconstitution may also be appropriate.[19] Unopened vials of incobotulinumtoxinA can be stored at room temperature (<25°C),[20] but the other toxins require refrigeration (2° to 8°C).
4. Other criteria considered important were cost, and duration of action before a repeat procedure is required. The expert panel noted that the duration of clinical efficacy of the three reference BoNTAs is generally 3–4 months.[21]
5. IncobotulinumtoxinA was considered the agent with the highest reliability and reproducibility due to its low immunogenic potential and equal efficacy to onabotulinumtoxinA.
6. The main contraindications for toxin use were reported as pregnancy and lactation, certain autoimmune diseases, and neurological conditions such as myasthenia gravis and Lambert-Eaton syndrome. Immunosuppression was considered a relative contradiction.

Dilution and Diffusion

Approved indications for BoNTA formulations are restricted to the treatment of horizontal forehead lines, glabellar lines, and crow's feet (Table 1). The available BoNTA formulations are not bioequivalent or biosimilar; however, if a switch to a different BoNTA product is required, dose equivalency conversion ratios are available. One unit (U) of incobotulinumtoxinA equals 1 U of onabotulinumtoxinA,[22] while 1 U of onabotulinumtoxinA equals anywhere between 2.5 and 3.0 U of abobotulinumtoxinA.[23]

The area of a toxin's effects may be impacted by the volume of the injection and toxin dilution. While one study found no change in safety or efficacy with higher volume dilutions,[27] other researchers found that forehead lines could be affected up to 50% more when the toxin was diluted by a factor of five.[28] Additionally, it has been demonstrated that the occurrence of adverse effects increases with higher dilutions (for example, eyebrow and eyelid ptosis while treating glabellar rhytids), indicating a greater diffusion of the toxin.[29]

Experts recommended reconstitution with bacteriostatic saline (if available), as it reduces pain during injection. On-label reconstitution volumes are 2.0–2.5 mL for 100 U and 1.0–1.25 mL for 50 U vials of incobotulinumtoxinA or onabotulinumtoxinA, and 2.5 mL for 500 U of abobotulinumtoxinA.

Table 1 FDA-Approved Indications and Manufacturer-Recommended Dosages of Botulinum Neurotoxin Products[24–26]

Non-Proprietary Name	FDA-Approved Indication	Dosage
AbobotulinumtoxinA	Glabellar lines	Total dose of 50 U divided among five sites (10 U each); retreatment no more frequently than every 12 weeks
OnabotulinumtoxinA	Glabellar lines	Total dose of 20 units divided among five injection sites (4 U each); repeat treatment every 12–16 weeks
	Lateral canthal lines	Total dose of 24 U divided among three injection sites on each side of face (4 U), six total injection points.
	Horizontal forehead lines	Total of 40 U divided among five forehead line sites (4 U each) and five glabellar line sites (4 U each).
IncobotulinumtoxinA	Glabellar lines	Total dose of 20 units divided among five sites; repeat no more frequently than every 12 weeks
	Lateral canthal lines	Total dose of 24 U divided among three injection sites on each side of face (4 U), six total injection points.
	Horizontal forehead lines	Total dose of 10–20 U divided among five horizontally aligned injection sites (2 U, 3 U, or 4 U, per injection point).

1. No benefit to higher dilution for standard neuromodulation was noted as it could lead to less accurate outcomes and increase side effects. Higher dilution with preserved sodium chloride 0.9% is off label, but widely used to reduce pain and may play a role in non-muscular (cutaneous) indications, for example to improve skin quality by reducing pore size in patients with oily to combination skin or seborrhea, and in the treatment of rosacea.
2. The general consensus for the three main toxins (incobotulinumtoxinA, onabotulinumtoxinA and abobotulinumtoxinA) was that diffusion depends on the amount of saline dilution used, the area that is being injected, and the number of units injected.

Pre-Operative Counselling in the Middle East

Effective patient-physician communication is critical in achieving a satisfactory aesthetic experience, and it plays a significant role in determining whether patients will return for future treatments. Pre-operative counseling serves several purposes. It establishes a rapport between the patient and the practitioner, who can explain why a particular treatment is recommended. The physician can discuss skin quality and address issues such as sun damage, wrinkles, and spots. The patient can also be made aware of any asymmetry and the need for harmony between facial structures. By explaining how a patient's facial anatomy can affect a particular feature, the patient can understand why specific treatments are required.

A thorough patient evaluation and the setting of realistic expectations during consultation are essential for achieving optimal outcomes and patient satisfaction. Experts recommended that physicians look for specific clinical findings that may affect treatment results, such as asymmetry, pre-existing brow ptosis, lid ptosis, brow shape, and malar edema. Evaluations should be performed with the patient at rest and during animation, including squinting, frowning, and elevating the eyebrows, to assess degree of muscle contraction, size, thickness, and depth of the target muscle beneath the skin. This should be repeated throughout the procedure to observe muscle action, which is crucial in determining injection points and dosages.

Prior to treatment, physicians should also discuss the rationale for treatment, mode of action, risks, benefits, and alternatives of BoNTA with the patient, explaining where the injection sites will be and that multiple injections may be required, and the risk of immunogenicity. This information should also be provided in written format and no treatment should be started before the patient has been provided with verbal and written information and she/he has provided signed consent. There are no regulations, restrictions or guidance instructions relating to the treatment of patients who are fasting, but general consensus was that BoNTA treatment does not compromise fasting.

Treatment Indications and Anatomical Considerations

Treatment with BoNTA is effective for dynamic wrinkles, regardless of a patient's age gender or ethnicity. However, darker skin tones are less susceptible to sun-induced damage so lines, wrinkles and loss of skin elasticity are less severe and typically occur 10–20 years later than in age-matched caucasian counterparts.[30,31] Darker skin has thicker and more compact dermis than white skin with the thickness proportional to the degree of pigmentation.[32] In addition, darker skin types are thought to have more cornified cell layers and greater lipid content compared to white stratum corneum.[33]

The general consensus was that more patients were asking for natural-looking results. A few years back the preference was for a very frozen look and shiny forehead, especially in women. This has changed, and patients now want a more relaxed and refreshed look, as opposed to a "frozen" upper face.

In individuals of Middle Eastern descent, the focus for toxin treatment is the upper face and in particular brow lifting, imparting a more youthful shape. Smoothing out of horizontal forehead and glabellar frown lines, and widening the eye are also frequently requested.[34] Treatment of lateral periorbital lines (crow's feet) is less in demand, but still required due to the variety of ethnic groups in the region and differences in skin type.[35] The effects of sun damage may also vary due to different requirements for covering of the face and neck in countries of the Middle East.[3,36] Micro-toxin injections and meso-toxin (toxin combined with HA) are also popular. A smaller percentage requests lower face injections, mostly to the masseter muscle and platysma (Nefertiti lift and vertical platysmal neck bands).[37]

Before any treatment, muscular pattern and strength must be evaluated so that treatment can be individualized and outcomes optimized. Injection points and units should follow those recommended in the individual neuromodulator's instructions for use.

However, it should be noted that standard doses and injection points may not meet the needs of all patients or address asymmetry, and dosing may need to be adjusted to match the intensity of contractions along the length of the muscle (Table 2). Neuromodulator dose is determined based on muscle strength and not race. Number of injection points reflects the pattern of wrinkles based on an individual's muscle movement. Men usually need a higher dose. People with oily and combination skin, and men generally need deeper injections. A further consideration is the timing of BoNTA injections in terms of an overall treatment plan as some procedures, for example radiofrequency or microfocused ultrasound, might decrease or shorten neuromodulator effectiveness.

To increase accuracy and reduce waste, the majority of experts use an insulin syringe which has no hub. A maximum of three injections per syringe was recommended as the small needles blunt rapidly. Some experts preferred a 33+ gauge needle (Invisible Needle, TSK Lab) with Luer-Lok 1 cc syringe, which can perform up to 16 injections.

Off-Label and Special Uses

BoNTA can be used in several off-label indications of interest for dermatologists.[10] The panel of experts agreed that there is enough evidence and practice for these off-label uses to be justified.[38–42]

These indications apply to areas of the mid and lower face and include treatment of the masseter, the platysma, the parotid, the submandibular gland, off-label parts of the orbicularis oculi nasalis, levator labii superioris alaeque nasi, temporoparietalis muscle, depressor anguli oris, depressor septi muscle, nasal flare with treatment of both the dilator and depressor parts of nasalis. BoNTA can also be injected into the orbicularis oris muscle of the upper lip to evert the lip, commonly referred to as "lip flip", and make it appear fuller without adding volume. Microinjections of BoNTA can also be used to control oily skin, reduce pore size, sebum production and acne, as well as for skin conditions such as rosacea. Injection protocols for the most common off-label indications are outlined below and in Table 3.

Table 2 Injection Techniques for On-Label Indications

Indication	Dose Range	Injection Plane	Technique
Medial glabellar complex	8–10 U 1U/side	Deep (corrugator supercilii and depressor supercilii). Superficial (corrugator tail)	Inject deep targeting both the corrugator supercilii and depressor supercilii muscles. Diffusion from these injection sites takes care of the procerus muscle. The latter is only injected when there is a deep horizontal line and heavy central bulging of procerus. In this case the procerus is injected with 4–8 U. The tails of the corrugators are also injected laterally, very superficial almost intradermally 1 U each side.
Frontalis	16–20 U (2–3 U per site)	Intramuscular	Tailor according to pattern of wrinkles and muscle strength. Avoid injecting lower half of frontalis, especially above the lateral third of brows. If necessary to inject, use 0.25 U or less.
Crow's feet	12–14 U/side	Superficial	Mark the skin according to the movement pattern. Dose reflects strength of orbicularis oculi muscles: full fan pattern, upper fan pattern, lower fan pattern or single line radiating from the lateral canthus. Start by injecting upper fibers of orbicularis oculi, where medial two-thirds of the brow meets lateral one third and inject 2–3U. 3–4U is injected on the line joining lateral canthus with the orbital bone (injection point is 1 cm lateral to the bone). Upper fan needs 2–3U, lower fan pattern also needs 2–3U.

Table 3 Injection Techniques for Popular Off-Label Indications

Indication	Dose Range	Depth	Technique
Nasal rhytids (bunny lines)	3–4 U	Superficial	Inject high up on the nose, to the sides of the bridge of the nose and into the area of maximum wrinkling. Inject superficially into skin overlying nasalis muscle.
Cobblestone chin	3–4 U	Deep	Inject two points adjacent to midline close to origin of mentalis muscle.
Changing eye silhouette to almond shape	1 U	Superficial	Inject into the center of the lower lash-line into the pretarsal section of the orbicularis oculi muscle. This creates widening of the eye. As the muscle relaxes, the eye becomes more oval or almond shaped.
Changing brow shape	2–3 U per injection point	Superficial	Inject 3 points on the orbicularis oculi: (1) First injection site medial two thirds of brow meeting lateral third of brow (3 U); (2) second injection site 2–3 cm lateral and 1 cm inferior to first injection point, just under hairy part of eyebrow (2U); (3) third injection point on line joining lateral canthus with orbital bone, 1 cm lateral to the bone (3–4U). Also inject two to three points on uppermost fibers of the frontalis muscle close to the hairline (1U each injection site) to induce the compensation force of the lower lateral frontalis muscle fibers.
Raise corners of mouth	3–4 U/side	Muscular	Inject origin of depressor anguli oris muscle at the level of the mandible.
Platysmal bands	3–5 U per injection point	Deep	Inject 3–5 U into each injection site tracing the bands from mandible to the clavicle.
Improving skin quality	0.25 U or less per injection point	Intradermal	Hyperdilute by mixing 10 U neurotoxin with 1–2 mL normal saline or lidocaine. Inject intradermally avoiding areas of origin or insertion of muscles of facial movement.

Nasal Rhytids (Bunny Lines)

"Bunny lines" is the common name given to wrinkles on the upper part of the nose that are formed by flexion of the fibers of the upper nasalis muscle, levator labii superioris alaeque nasi muscle and secondarily by the medial muscular band of the orbicularis oculi muscle.[43] The middle portion of the procerus and the depressor supercilii also contribute to these wrinkles.[44] Treatment of bunny lines is tailored according to the patient because they differ from one individual to another. Injection points should be marked where the strongest lines form. Experts recommended holding the bulk of the muscle between thumb and forefinger and pushing up to create more thickness. The nasalis is then treated with a maximum of 4U injected into the muscle in two injection points (2U on either side). Injections are superficial into the dermis. Some experts also inject the depressor supercilii (2U per side) as a recent article has shown that improvement in nasal rhytids occurs when this muscle is relaxed.[44] Care must be taken not to inject too laterally to avoid the levator labii superioris alaeque nasi muscle that runs down the side of the nose to the upper lip, and which if affected can cause the upper lip to droop.

Dimpled Chin Due to Mentalis Muscle Contraction

The expert group agreed that injection of the mentalis is a much requested treatment and delivers very satisfying results to patients. Injecting the mentalis decreases skin dimpling and relaxes the look of the chin as well as the mental crease.[45] In order to deliver optimal results, injectors should study the movement of the mentalis muscle and decide which pattern of injections will deliver optimal results. Three types of mentalis muscle morphology have been described in the literature: (i) two bilateral mentalis muscles bellies running vertical and merging at the bottom to make a V-shape (47%); (ii) two muscle bellies running parallel and completely separated (38%); and (iii) a flat and thin mentalis comprised of only a few muscle fibers (13%); the latter pattern does not warrant

treatment with toxin.[46] Three techniques were recommended depending on the individual anatomy. The first advocates deep injections in the mentalis muscle at a point 5 mm to the left and right of the pogonion. The mentalis muscle is located at mean depths of 6.7 to 10.7 mm below the skin surface.[46] A second technique dictates injecting one point deep in the center of the chin only. A third technique is to inject intradermally.

Correction of Corners of Mouth

Downturned corners of the mouth can give an individual a sad or angry appearance. The experts recommended a one point injection of 4U per side in the depressor anguli oris muscle belly at around 4 mm depth, taking care to avoid spread of neurotoxin to adjacent muscles.[47]

Jawline Shaping

The shape of the jawline can be improved using a five-point injection technique of 2U along the length of the jawline, injecting into the platysma muscle at a depth of 3 mm.

Gummy Smile

A gummy smile can be classified into "anterior gummy smile" or "mixed gummy smile". Typically a dose of 2–8 U is used on each side; the dose is determined in proportion with the amount of gum visibility and type of gummy smile.

To treat the anterior gummy smile, the levator labiisuperioris alaeque nasi (LLSAN) and levator labii superioris (LLS), which extend from the sides of the nose to the upper lips, are relaxed. This is achieved by injecting in the upper part of the nasolabial fold 1 cm lateral to the ala of the nose. Here, 2–4 U are injected per side according to the amount of gum show. A general rule of injection dosage in this area is 1 U for 1 mm of gum show and 4 U for 4 mm of gum show.

To treat a mixed gummy smile the LLSAN, zygomaticus major (ZM), and zygomaticus minor (ZMn) muscles are relaxed. The LLSAN is injected as above, as well as two other points corresponding to the insertion of the zygomaticus muscles. These are at a point slightly above the deepest point of contraction at the nasolabial fold, and midway between the ala of the nose and the oral commissure at the level of the lower edge of the tragus. A dose of 1–2 U is injected in both these points to tone down the pull of the ZM and ZMn on the lips.

Lip Flip

As the orbicularis oris is a sphincter muscle that closes the oral cavity, injecting this muscle at strategic points relaxes the muscle making the lips plumper and creating a more everted look. As a very conservative approach, inject 2 U only; 1 U on each side of the cupid's bow. Pierce the skin 1 mm above the vermillion border, 2–3 mm lateral from the philtrum line joining the lip vertex and deposit 1 U. Injection depth should be 1–2 mm. If the client requests more eversion add 2 U more; 1 U on each side 3–4 mm away from the first injection point, and staying 1 mm above the vermillion border.

High-Dose Recommendations

Interest in optimizing outcomes, maximizing treatment duration, and improving efficacy has prompted the study of high-dose BoNTA treatment. The expert panel reviewed the evidence as to whether the observed improvements in treatment duration and patient satisfaction warrant treatment with high-dose regimens delivered as high-concentration injections. Several studies and a consensus paper have reported that administering increased BoNTA doses in small volumes allows for natural outcomes and does not increase the potential for a `frozen` appearance.[48–50] High-dose studies have also shown that delivery of more concentrated doses was associated with a longer duration of effect than the same total dose delivered in a higher volume of solvent. Furthermore, across all high-dose studies, treatment-emergent adverse events were not significantly higher among patients in high-dose groups as compared with standard-dose groups. It is not known if higher concentrations administered less often will be more or less immunogenic than standard protocols.

The experts agreed that higher dose treatments extended duration of effect without increased safety issues or a reduction in patient satisfaction. One study has reported that a five-fold increase in the on-label dose of incobotulinumtoxinA was associated with a median response duration of around 9 months.[48] A similar increased response duration was observed by a 2 to 2.5-fold increase in the on-label dose of abobotulinumtoxinA and 2 to

4-fold increase in on-label dose of onabotulinumtoxinA. Importantly, the extended duration of effect at higher doses did not compromise natural-looking results.

Post-Treatment Advice

It was the experts' belief that complicated post-treatment instructions may alarm some patients and cause undue anxiety. They recommended that post-treatment advice should be kept clear and simple and reflect that in the individual BoNTA instructions for use. These include:

1. Avoidance of heavy physical activities or exercise, especially in the next 40 minutes.
2. No massage of treated areas for 2h.
3. No application of make-up immediately after injection. If patients choose not to follow this piece of advice, they should use a sealed makeup so that the risk of contamination is lower.

Conclusions

Botulinum toxin use is gaining popularity rapidly and so are its on- and off-label indications. This consensus reflects the experience of expert BoNTA injectors in the Middle East. Although it is bespoke to the region's variability of patients' features and requirements, the consensus is valid for wider global practice. It also reflects current clinical practice, where there is a move away from standardized templates for injection sites and doses toward tailored treatment, taking into account individual facial anatomy, patterns and strength of muscle activity, and patient and ethnic preferences. Expert injectors continue to expand the potential uses for BoNTA with additional off-label indications and new techniques for diluting and injecting at different tissue depths. Such procedures often lead to better procedures and outcomes, and practitioners are encouraged to build up evidence to allow these innovations to move to new on-label recommendations.

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References

1. International Society of Aesthetic Plastic Surgery (ISAPS). ISAPS international survey on aesthetic/cosmetic procedures performed in 2019. Available from: https://www.isaps.org/wp-content/uploads/2020/12/Global-Survey-2019.pdf. Accessed January 8, 2023.
2. The middle east population; 2022. Available from: https://worldpopulationreview.com/continents/the-middle-east-population. Accessed June 16, 2022.
3. Kashmar M, Alsufyani MA, Ghalamkarpour F, et al. Consensus opinions on facial beauty and implications for aesthetic treatment in Middle Eastern women. *Plast Reconstr Surg Glob Open*. 2019;7(4):e2220. doi:10.1097/GOX.0000000000002220
4. Yutskovskaya Y, Gubanova E, Khrustaleva I, et al. IncobotulinumtoxinA in aesthetics: Russian multidisciplinary expert consensus recommendations. *Clin Cosmet Investig Dermatol*. 2015;8:297–306. doi:10.2147/CCID.S72301
5. Sundaram H, Huang PH, Hsu NJ, et al; Pan-Asian Aesthetics Toxin Consensus Group. Aesthetic applications of botulinum toxin A in Asians: an international, multidisciplinary, pan-asian consensus. *Plast Reconstr Surg Glob Open*. 2016;4(12):e872. doi:10.1097/GOX.0000000000000507
6. Sundaram H, Signorini M, Liew S, et al.; Global Aesthetics Consensus Group. Global aesthetics consensus: botulinum toxin type a--evidence-based review, emerging concepts, and consensus recommendations for aesthetic use, including updates on complications. *Plast Reconstr Surg*. 2016;137 (3):518e–529e. doi:10.1097/01.prs.0000475758.63709.23
7. Farkas LG, Katic MJ, Forrest CR, et al. International anthropometric study of facial morphology in various ethnic groups/races. *J Craniofac Surg*. 2005;16(4):615–646. doi:10.1097/01.scs.0000171847.58031.9e
8. Al-Sebaei MO. The validity of three neo-classical facial canons in young adults originating from the Arabian Peninsula. *Head Face Med*. 2015;11 (1):4. doi:10.1186/s13005-015-0064-y
9. El Minawi H, El Saloussy Y, Sabry M, Wahdan W, El Sharkawy O. Facial anthropometry and analysis in Egyptian women. *Plast Reconstr Surg Glob Open*. 2022;10(5):e4333. doi:10.1097/GOX.0000000000004333
10. Samizadeh S, De Boulle K. Botulinum neurotoxin formulations: overcoming the confusion. *Clin Cosmet Investig Dermatol*. 2018;11:273–287. doi:10.2147/CCID.S156851

11. Kerscher M, Roll S, Becker A, Wigger-Alberti W. Comparison of the spread of three botulinum toxin type A preparations. *Arch Dermatol Res*. 2012;304(2):155–161. doi:10.1007/s00403-011-1179-z
12. Grein S, Mander GJ, Fink K. Stability of botulinum neurotoxin type A, devoid of complexing proteins. *Botulinum J*. 2011;2(1):49–58. doi:10.1504/TBJ.2011.041815
13. Carr WW, Jain N, Sublett JW. Immunogenicity of botulinum toxin formulations: potential therapeutic implications. *Adv Ther*. 2021;38(10):5046–5064. doi:10.1007/s12325-021-01882-9
14. Fathallah AM, Bankert RB, Balu-Iyer SV. Immunogenicity of subcutaneously administered therapeutic proteins--a mechanistic perspective. *AAPS J*. 2013;15(4):897–900. doi:10.1208/s12248-013-9510-6
15. Bellows S, Jankovic J. Immunogenicity associated with botulinum toxin treatment. *Toxins*. 2019;11(9):491. doi:10.3390/toxins11090491
16. Kerscher M, Wanitphakdeedecha R, Trindade de Almeida A, Maas C, Frevert J. IncobotulinumtoxinA: a highly purified and precisely manufactured botulinum neurotoxin type A. *J Drugs Dermatol*. 2019;18(1):52–57.
17. Carey WD. Incorrect reconstitution of incobotulinumtoxinA leads to loss of neurotoxin. *J Drugs Dermatol*. 2014;13(6):735–738.
18. Niamtu J. Neurotoxin waste from drawing product through the vial stopper. *J Clin Aesthet Dermatol*. 2014;7(6):33–37.
19. Thomas JP, Siupsinskiene N. Frozen versus fresh reconstituted botox for laryngeal dystonia. *Otolaryngol Head Neck Surg*. 2006;135(2):204–208. doi:10.1016/j.otohns.2006.04.001
20. Soares DJ, Dejoseph LM, Zuliani GF, Liebertz DJ, Patel VS. Impact of postreconstitution room temperature storage on the efficacy of incobotulinumtoxinA treatment of dynamic lateral canthus lines. *Dermatol Surg*. 2015;41(6):712–717. doi:10.1097/DSS.0000000000000365
21. Wright G, Lax A, Mehta SB. A review of the longevity of effect of botulinum toxin in wrinkle treatments. *Br Dent J*. 2018;224(4):255–260. doi:10.1038/sj.bdj.2018.126
22. Frevert J. Pharmaceutical, biological, and clinical properties of botulinum neurotoxin type A products. *Drugs R D*. 2015;15(1):1–9. doi:10.1007/s40268-014-0077-1
23. Car H, Bogucki A, Bonikowski M, et al. Botulinum toxin type-A preparations are not the same medications — basic science (Part 1). *Neurol Neurochir Pol*. 2021;55(2):133–140. doi:10.5603/PJNNS.a2021.0027
24. DYSPORT® Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125274s107lbl.pdf. Accessed October 3, 2023.
25. BOTOX© Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103000s5232lbl.pdf. Accessed October 3, 2023.
26. XEOMIN© Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125360s078lbl.pdf. Accessed October 3, 2023.
27. Carruthers A, Carruthers J, Cohen JL. Dilution volume of botulinum toxin type A for the treatment of glabellar rhytides: does it matter? *Dermatol Surg*. 2007;33(1):S97–S104. doi:10.1111/j.1524-4725.2006.32339.x
28. Trindade De Almeida AR, Secco LC, Carruthers A. Higher dilution associated with higher diffusion and less efficacy. Handling botulinum toxins: an updated literature review. *Dermatol Surg*. 2011;37(H):1553–1565. doi:10.1111/j.1524-4725.2011.02087.x
29. Cohen JL, Ozog DM, Editors. *Botulinum Toxins: Cosmetic and Clinical Applications*. First ed. JohnWiley & Sons Ltd; 2017. Available from: www.wiley.com/go/cohen/botulinum. Accessed October 3, 2023.
30. Kaidbey KH, Agin PP, Sayre RM, Kligman AM. Photoprotection by melanin, a comparison of black and Caucasian skin. *J Am Acad Dermatol*. 1979;1(3):249–260. doi:10.1016/S0190-9622(79)70018-1
31. Hexsel DM, Hexsel CL, Brunetto LI. Botulinum toxin. In: Grimes PE, editor. *Aesthetic and Cosmetic Surgery for Darker Skin Types*. Philadelphia, PA: Lippincott Williams and Wilkins; 2008:211–224.
32. Montagna W, Prota G, Kenney J. The structure of black skin. In: Montagna W, Prota G, Kenney J, editors. *Black Skin Structure and Function*. Gulf Professional Publishing; 1993.
33. Sugino K, Imokawa G, Maibach H. Ethnic differences in stratum corneum lipid in relation to stratum corneum function. *J Invest Dermatol*. 1993;100:594.
34. Yi KH, Lee JH, Hu HW, Kim HJ. Anatomical proposal for botulinum neurotoxin injection for glabellar frown lines. *Toxins*. 2022;14(4):268. doi:10.3390/toxins14040268
35. Yi KH, Lee JH, Kim GY, Yoon SW, Oh W, Kim HJ. Novel anatomical proposal for botulinum neurotoxin injection targeting lateral canthal rhytids. *Toxins*. 2022;14(7):462. doi:10.3390/toxins14070462
36. Amiri L, Galadari H, Al Mugaddam F, Souid AK, Stip E, Javaid SF. Perception of cosmetic procedures among Middle Eastern Youth. *J Clin Aesthet Dermatol*. 2021;14(12):E74–E83.
37. Yi KH, Lee JH, Lee K, Hu HW, Lee HJ, Kim HJ. Anatomical proposal for botulinum neurotoxin injection targeting the platysma muscle for treating platysmal band and jawline lifting: a review. *Toxins*. 2022;14(12):868. doi:10.3390/toxins14120868
38. Phan K, Younessi S, Dubin D, Lin MJ, Khorasani H. Emerging off-label esthetic uses of botulinum toxin in dermatology. *Dermatol Ther*. 2022;35(1):e15205. doi:10.1111/dth.15205
39. Baker A. Off-label cosmetic use of botulinum toxin in the lower face. Pmfa News|February/March 2016|Vol 3 No 3; 2016.
40. Munavalli GS, Benedetto AV, Biesman BS, Cutler Peck CM. Treatment of the periocular area – crow's feet, brow, and bunny lines. In: Cohen JL, Ozog DM, editors. *Botulinum Toxins: Cosmetic and Clinical Applications*. Wiley Online Library;2017. doi:10.1002/9781118661833.ch12
41. Shirshakova M, Morozova E, Sokolova D, Pervykh S, Smirnova L. The effectiveness of botulinum toxin type A (BTX-A) in the treatment of facial skin oily seborrhea, enlarged pores, and symptom complex of post-acne. *Int J Dermatol*. 2021;60(10):1232–1241. doi:10.1111/ijd.15574
42. Allen S, Sengelmann R, Simmons R. Treatment of the perioral area. In: Cohen JL, Ozog DM, editors. *Botulinum Toxins: Cosmetic and Clinical Applications*. Wiley Online Library;2017. doi:10.1002/9781118661833.ch14
43. Yi KY, Lee JH, Hu HW, Kim HJ. Novel anatomical guidelines on botulinum neurotoxin injection for wrinkles in the nose region. *Toxins*. 2022;14(5):342. doi:10.3390/toxins14050342
44. Hur MS, Lee S, Jung HS, Schneider RA, Cray JJ. Anatomical connections among the depressor supercilii, levator labii superioris alaeque nasi, and inferior fibers of orbicularis oculi: implications for variation in human facial expressions. *PLoS One*. 2022;17(3):e0264148. doi:10.1371/journal.pone.0264148

45. Yi KH, Lee JH, Hu HW, et al. Novel anatomical guidelines for botulinum neurotoxin injection in the mentalis muscle: a review. *Anat Cell Biol*. 2023;56(3):293–298. doi:10.5115/acb.22.266
46. Choi DY, Bae H, Bae JH, Kim HJ, Hu KS. Effective locations for injecting botulinum toxin into the mentalis muscle; cadaveric and ultrasonographic study. *Toxins*. 2021;13(2):96. doi:10.3390/toxins13020096
47. Yi KH, Lee JH, Hu HW, et al. Novel anatomical proposal for botulinum neurotoxin injection targeting depressor anguli oris for treating drooping mouth corner. *Anat Cell Biol*. 2023;56(2):161–165. doi:10.5115/acb.22.258
48. Kaufman-Janette J, Cox SE, Dayan S, Joseph J. Botulinum toxin type a for glabellar frown lines: what impact of higher doses on outcomes? *Toxins*. 2021;13(7):494. doi:10.3390/toxins13070494
49. Dayan S, Joseph J, Moradi A, et al. Subject satisfaction and psychological well-being with escalating abobotulinumtoxinA injection dose for the treatment of moderate to severe glabellar lines. *J Cosmet Dermatol*. 2022;21(6):2407–2416. doi:10.1111/jocd.14906
50. Fabi SG, Carruthers J, Joseph J, et al. High-dose neuromodulators: a roundtable on making sense of the data in real-world clinical practice. *Aesthet Surg J Open Forum*. 2021;3(4):ojab036. doi:10.1093/asjof/ojab036