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toxins

Botulinum toxin in aesthetic medicine: injection protocols and complication management

Jani van Loghem

general background

Theoretical overview of botulinum toxin history and mechanism of action

facial indications

Standard injection protocols for botulinum toxin indications in the face

non-facial indications

Botulinum toxin treatment protocols for body indications

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Know what can go wrong.
Know what can go right.
Know why something works, and when it won't.
Know the difference between good and great.
Know what a patient wants, and what they need.
Know when to push on. Know when to stop.
Know why you're being cautious, or brave.
Know what you don't know.
Know more than the products in your dispensary.
Know more than the treatments you offer,
or the tools you use to deliver them.
Know how to express who your patient wants to be.

knowledge is beautiful

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let's talk botulinum toxin

Injection Protocols and Complication Management

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introduction

Dear colleagues,

As the field of aesthetic medicine grows, more and more aesthetic physicians seek structured education in order to optimize the safety and quality of the treatments they offer. I enjoy being a trainer and educator as much as I enjoy treating my patients and feel an obligation to share my experience and practical tips with my fellow aesthetic physicians. I have therefore started UMA Academy as a basis for quality aesthetic education, focusing predominantly on hands-on training.

Protocols

As protocols and standardized treatments play an increasingly important part in the development of aesthetic medicine as a medical field, various consensus papers have been published to provide physicians with standard protocols for botulinum toxin injection therapy. The protocols described here have been developed using consensus recommendations from a number of consensus groups and various publications published by the Dutch Society of Aesthetic Medicine, the Deutsche Gesellschaft für Dermatologie, The European Academy of Dermatology and Venereology, The American Society for Dermatologic Surgery, The American Academy of Otolaryngology, Head and Neck Surgery, and the American Academy of Cosmetic Surgery. For the final recommendations in these standard protocols, we, the physicians of UMA Institute, have adjusted the injection patterns and doses slightly to optimize efficacy, while minimizing risks of side effects.

eBook

This practical book is meant for quick review during day-to-day practice in aesthetic medicine. We have included limited background information about botulinum toxin: the history, mechanism of action, the different available products with similarities and differences, reconstitution, patient consultation, documentation and photography, physical examination, marking and preparing for injection. More emphasis is placed on practical uses of botulinum toxin such as injection patterns, relevant anatomy and avoiding and treating complications.

The use of Bocouture® (Xeomin®)

In our clinic, we use IncobotulinumtoxinA (Bocouture® / Xeomin®; Merz Aesthetics GmbH, Frankfurt, Germany). The reason for this choice is that we do not introduce an unnecessary risk of immunogenicity to our patients as this product is free from complexing proteins. For patients who are very keen on having natural results, we have introduced a new way of treating with this product which uses only half the recommended doses shown in the protocols in this book. Of course, this reduces duration, so we retreat these patients every 2-3 months instead of every 4 months. This provides a non-blocked, more subtle refreshed and relaxed result and is typically what many of our patients want nowadays. Bocouture®/ Xeomin® is the only toxin that can be used with such short treatment intervals. Other patients prefer a more blocked effect with very long duration. For these individuals, the recommended dose may be increased up to 5 times, keeping in mind that the risk of side effects increases. In this book we also discuss OnabotulinumtoxinA (Vistabel®/ Botox®; Allergan Inc., Irvine, CA, USA) and AbobotulinumtoxinA (Azzalure®/ Dysport®; Ipsen, Paris, France) and provide recommended doses and injection schemes.

We hope this book will be of value to you, your clinic and your patients. Please let us know if you have any ideas for improvement as we would love to hear from you.

Jani van Loghem, MD PhD
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01
general background

introduction

Apart from theoretical and practical knowhow, a broad understanding of all aesthetic treatment methods is a requirement for the practitioner to safely offer botulinum toxin treatment and to assess whether this treatment is the first choice for the patient requesting botulinum toxin therapy.

Besides a medical degree, a well-structured training program that assesses both the theoretical and practical skills of the practitioner is a prerequisite for the botulinum toxin injector.

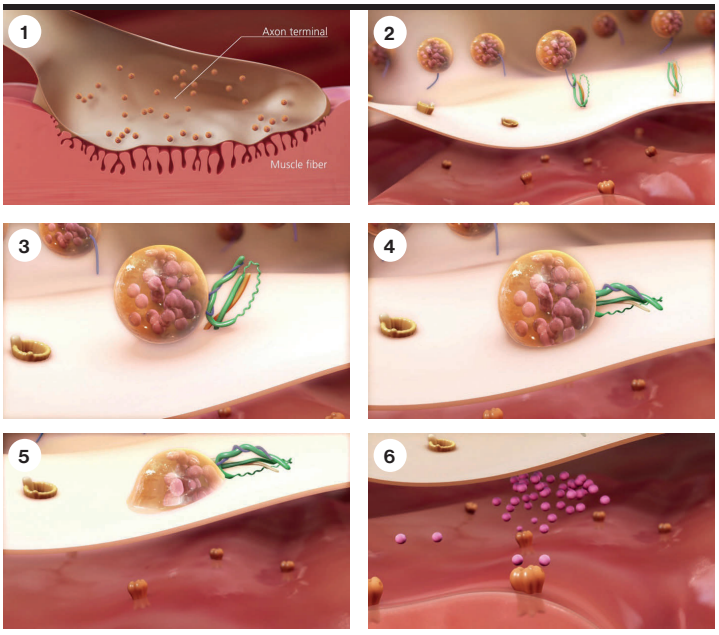
general

1.1 History of botulinum toxin

In 1817, Dr. Justinus Kerner described the disease botulism, a serious form of food poisoning, resulting in symmetric overall muscle paralysis leading to death. The likely cause of this condition in the publication of Kerner was identified as spoiled sausages. Kerner concluded from his research that a diluted form of the poison could be used in the treatment of patients with muscular hyper-motility disorders. Further research on botulism led to the isolation of *Clostridium Botulinum* which is a large, spore-forming, anaerobic bacterium. This was followed by the isolation of botulinum toxin type A and subsequent clinical testing and application in hyperkinetic disorders, including blepharospasm and strabismus. In 1992, the Canadian couple Jean (ophthalmologist) and Alistair (dermatologist) Carruthers published the first scientific study about botulinum toxin for the aesthetic treatment of the glabella. Patients that were treated for blepharo-spasm showed a reduction of dynamic wrinkles. This observation had a huge impact on the world of aesthetic medicine and botulinum toxin is now the most important instrument of many aesthetic practitioners.

1.2 Mechanism of action

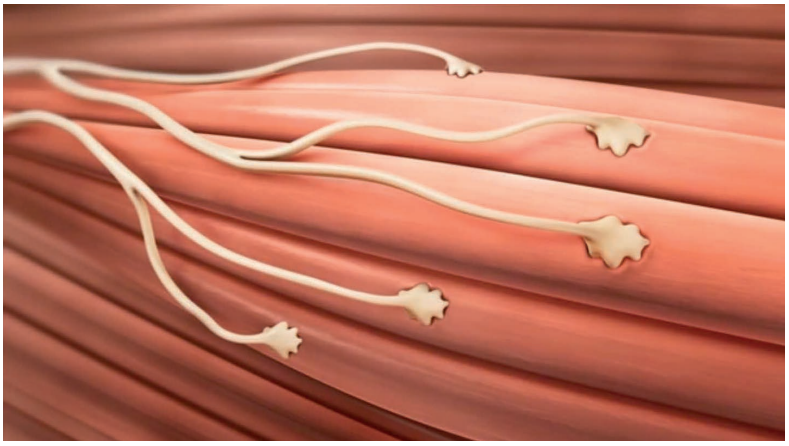
The protein botulinum toxin is a double chain poly-peptide molecule that is produced by the bacterium *Clostridium Botulinum*. It consists of a light chain (50kD) and a heavy chain (100 kD). After injection, the botulinum toxin protein binds with the heavy chain to presynaptic receptor SV1 and endocytosis occurs. The heavy chain forms a pore in the membrane of the endocytosis vacuole so that the short-chain can be released into the cytoplasm, and exert its pharmacological effect. Seven different variants are known (type A to G), of which type A is the most potent. The mechanism of action of all variants is based on blocking the signal from the neuronal axon to the neuromuscular junction by preventing fusion of the acetylcholine neurotransmitter vacuoles with the presynaptic membrane. The different variants of botulinum toxin target a different presynaptic protein. Botulinum toxin type A selectively targets SNAP-25, part of the SNARE complex and one of the intracellular presynaptic proteins that is essential for fusing acetyl choline vacuoles with the presynaptic membrane after the electric stimulus reaches the end of the axon.
With SNAP-25 cleaved by the light chain, the SNARE complex doesn't work, the acetyl choline vacuole cannot fuse, and therefore the neurotransmitter will remain intracellular instead of reaching the synapse. The motor neuron is then blocked for approximately 3-4 months.



Images kindly provided by Merz Aesthetics

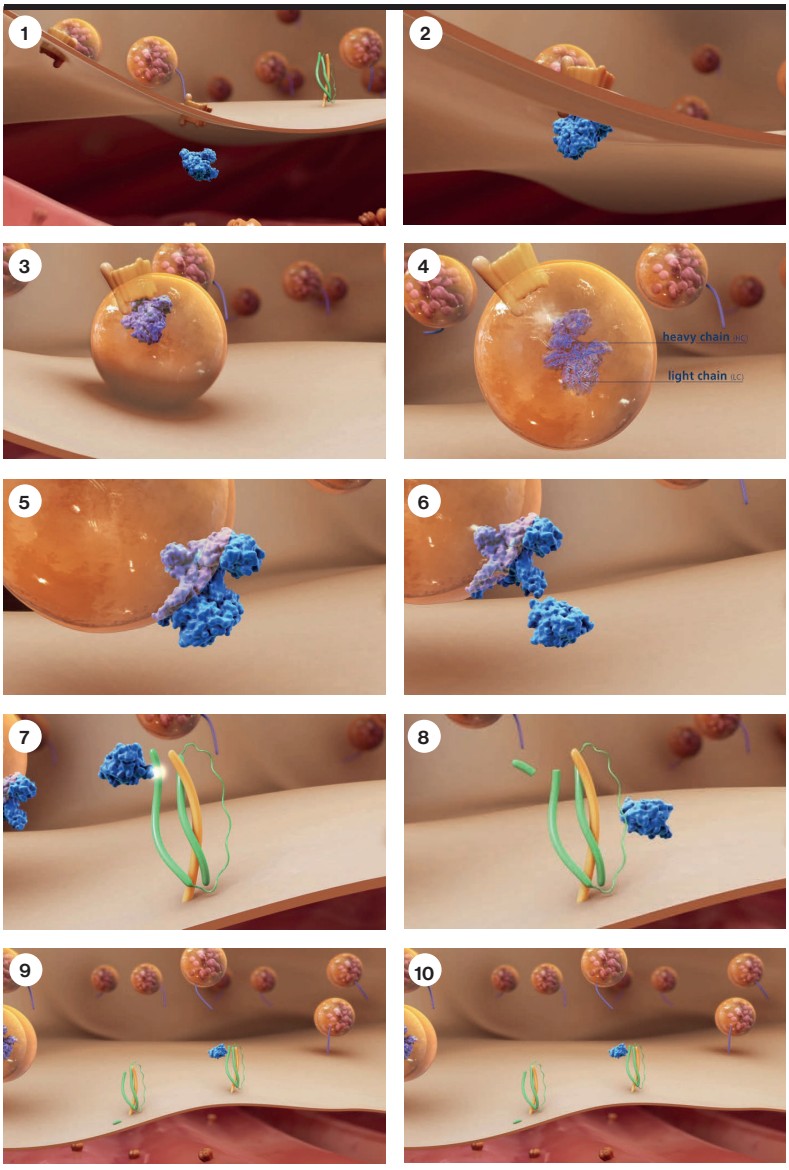
Figure 1
Mechanism of action of botulinum toxin type A

1 The axon of the motor nerve innervates the muscular fiber at the motor endplate. Inside the axon terminal, vacuoles of acetyl choline are stored.
2 After electric stimulus of the motor neuron, the acetyl choline vacuoles bind with the SNARE complex that is attached to the presynaptic membrane.
3 Binding of the vacuole to the SNARE complex results in conformational change, directing the vacuole to the membrane.
4 The vacuole fuses with the presynaptic membrane and its contents are released into the synaptic cleft.
5 The neurotransmitter acetyl choline diffuses to the postsynaptic membrane and binds to its target receptor, resulting in contraction of the muscle fiber.



Watch video at http://bit.ly/botulinum-toxin-in-aesthetic-medicine-uma-academy
Movie kindly provided by Merz Aesthetics

Video 1
Mechanism of action of botulinum toxin type A



Images kindly provided by Merz Aesthetics

Figure 2
Mechanism of action of botulinum toxin type A

1 The botulinum toxin dipeptide binds to the presynaptic membrane receptor SV2.
2 After binding, endocytosis is initiated.
3 An endocytosis vacuole is released from the plasma membrane and free in the cytosol.
4 The pH lowers and causes the heavy chain to dissociate from the light chain.
5 Due to the low pH, the heavy chain forms a transmembrane protein in the endocytosis vacuole membrane and allows the light chain to pass through its pore.
6 The light chain is released and diffuses freely through the cytosol.
7 The light chain specifically cleaves the SNAP-25 protein, which is part of the SNARE complex.
8 The light chain, being a protease, retains its activity after cleaving.
9 Additional SNAP-25 proteins are cleaved by the same light chain.
10 After electric stimulus of the motor neuron, no binding is possible with the SNARE complex due to the cleaved SNAP-25 protein. No nero-transmitter is released into the synaptic cleft and no muscular contraction is the result.

1.3 Training and continuing medical education

The Dutch Society of Aesthetic Medicine has developed a 2-year post-graduate medical profile specialty training program for physicians who want to specialize in aesthetic medicine. This full-time training program covers injectables, cosmetic dermatology, energy-based devices and (knowledge of) aesthetic surgery. The Dutch authorities have officially approved this training program as it is structured according to the CAN-MEDS system and therefore meets the highest standards of medical specialist training. As many countries do not have official specialist training in aesthetic medicine or aesthetic botulinum toxin therapy, we advise practitioners to follow courses that assess theoretical and technical skills, and to keep a logbook as proof of experience, as legislation concerning who is allowed to perform these treatments is becoming stricter around the globe. Proof of knowledge of cosmetic surgery, fillers, biostimulators, threads, mesotherapy, platelet-rich plasma, needling, cosmeceuticals, dermato-pathology, chemical peels, lasers, intense-pulsed light, focused ultrasound and other energy-based devices is also strongly recommended in order to advise patients on the appropriate therapies and individualized treatment.

Maintaining theoretical knowledge and technical skills is a prerequisite for quality of care. A minimum number of treatments and days per week working with botulinum toxin can assure the quality of the practitioner. On average, the doctor should work at least 2 days per week in aesthetic medicine and treat at least 5 patients per week with botulinum toxin. Theoretical knowledge can be maintained by visiting aesthetic congresses, e-learning and workshops. Certificates of attendance should be kept as proof of the respective society's accreditation.

We advise practitioners to follow courses that assess theoretical and technical skills, and to keep a logbook as proof of experience, as legislation concerning who is allowed to perform these treatments is becoming stricter around the globe.

1.4 Manufacturers

There are three manufacturers who have marketed botulinum toxin type A (botulinum toxin) in Europe. Each of the manufacturers has a product with registration for neurological indications as well as a product for cosmetic indications (Table 1).

The different manufacturers all use the same strain of Clostridium Botulinum (the so-called "Hall strain") and therefore, in principle, produce the same botulinum toxin type A molecule. The pharmacologically active protein should therefore be identical in these products and the same clinical effects should be achieved. However, there are variations in the production process so that the final products are different from each other. The Merz Aesthetics products, Bocouture® and Xeomin®, are free from complexing proteins, containing only the core botulinum neurotoxin type A. The products of Allergan and Ipsen contain botulinum neurotoxin type A and complexing proteins, which have no pharmaco-logical effect. When the these products are reconstituted in saline at physiological pH, the complexing proteins dissociate from the botulinum neurotoxin so that in all products, the free botulinum neurotoxin is present prior to injection.

The determination of units is undertaken by each manu-facturer with their own proprietary LD50 assay. These assays differ and therefore the units are not necessarily equal. Several studies suggest that the conversion factor between Merz and Allergan is 1:1 and between Allergan (or Merz) and Ipsen is 1:2.5. A striking difference is the amount of albumin per vial (see Table 1). It is possible that the relatively low amount of albumin in the Ipsen products Azzalure® and Dysport® is the reason why Ipsen units require a conversion factor.

Table 1
Manufacturers and botulinum toxin products
U: international units sU: Speywood units.

		Brand	Content	Indication
01	**Merz Aesthetics** Scientific name: IncobotulinumtoxinA	Bocouture®	50 U or 100 U per vial	Glabella Periorbital lines Horizontal forehead lines
		Xeomin®	100 U per vial	Neurological
02	**Allergan** Scientific name: OnabotulinumtoxinA	Vistabel®	50 U per vial	Glabella Periorbital lines Horizontal forehead lines
		Botox®	100 U per vial	Neurological
03	**Ipsen** Scientific name: AbobotulinumtoxinA	Azzalure®	125 sU per vial	Glabella Periorbital lines
		Dysport®	500 sU per vial	Neurological

Table 2
Product characteristics and differences

	Dysport® / Azzalure®	**Xeomin® / Bocouture®**	**Botox® / Vistabel®**
Active Ingredient	Botulinum neurotoxin type A	Botulinum neurotoxin type A	Botulinum neurotoxin type A
Other clostridial proteins	Hemagglutinin Proteins Flaggelin		Non-toxic, non-hemagglutinin proteins and hemagglutinin proteins
Molecular weight	500-900 kDa	150 kDa	900 kDa
Additional ingredients	Albumin 0.125 mg Lactose 2.5 mg	Albumin 1 mg Sucrose 4.7 mg	Albumin 0.5 mg NaCl 0.5 mg
Total proteins	ca. 4.35 ng/500 sU	ca. 0.44 ng/100 U	ca. 5 ng/100 U
Units conversion factor	1:2.5	1	1
Mechanism of action	SNAP-25	SNAP-25	SNAP-25
Official indications	Glabella, Lateral Periorbital lines	Glabella, Lateral Periorbital lines, Horizontal forehead lines	Glabella, Lateral Periorbital lines, Forehead lines
Product Form	Powder	Powder (freeze-dried)	Powder
Dosage per vial	125 Speywood U/vial	50 Merz U/vial 100 Merz U/vial	50 Allergan U/vial
Reconstitution	0.9% NaCl	0.9% NaCl	0.9% NaCl
Recommended number of units per 0.1 ml	20	4	4
Storage temperature unopened vial	Cooled: 2-8°C	Lower than 25°C	Cooled: 2-8°C
Shelf life unopened flacon	Not mentioned	36 months	36 months
Storage temperature after reconstitution	Cooled: 2-8°C	Cooled: 2-8°C	Cooled: 2-8°C
Shelf life after reconstitution	4 hours	24 hours	24 hours

1.5 Diffusion and spread of botulinum toxin products

Diffusion of botulinum toxin is about moving the molecules from the injection site, on the basis of the concentration difference of the botulinum toxin with respect to the surrounding tissue. The speed of diffusion of botulinum toxin is dependent on molecule size, and will stop after binding to its target receptor (SV2).

Several publications have shown differences in diffusion radii of botulinum toxin products; in particular, differences between the products of Ipsen and Allergan have been widely described. Ipsen appears to have a larger diffusion radius than the Allergan botulinum toxin. Allergan and Merz products have a similar diffusion profile. Due to the fact that, after reconstitution, the complexing proteins dissociate from the toxin within one minute, the expla-nations for differences in diffusion are not related to the molecular size of the protein complex; the 900 kDa molecule of Allergan has an identical diffusion profile to the 150 kDa molecule of Merz.

Spread of botulinum toxin is a clinical observation that differs from diffusion. Physical forces such as massage, injection techniques, dilution volumes, thickness and length of the injection needle, etc. influence spread. In one study, the three products were compared on the basis of their anhidrotic halo with the Azzalure® / Dysport® product appearing to have a larger spread than the other two products. Other studies indicate an equal distribution.

1.6 Reconstitution of botulinum toxin products

According to the instructions for use, the three different products must be reconstituted in physiologic saline solution (0.9% NaCl) to 0.1 ml per 4U (Merz and Allergan) or 20 sU (Ipsen). The medical literature has published various methods to make the injections less painful, such as adding lidocaine and using bacteriostatic saline (in which benzyl alcohol is added for an anesthetic effect).

1 **Reconstitution of Azzalure®**
0.63 ml saline (whether or not buffered) per vial of 125 sU in order to obtain a concentration of 5sU / 0.05 ml.

2 **Reconstitution of Vistabel®**
1.25 ml saline per vial of 50 U in order to obtain a concentration of 4U / 0.1 ml.

3 **Reconstitution of Bocouture®**
1.25 ml NaCl (whether or not buffered) per vial of 50U or 2.5 ml in a vial of 100U in order to obtain a concentration of 4U / 0.1 ml. For Bocouture® it is recommended to gently pivot the vial, and to make sure that the saline has touched all the surfaces on the inside of the vial, including the rubber cap. Due to the manufacturing proccess, the botulinum toxin can be anywhere in the vials, incluing the afore mentioned surfaces. If, after reconstitution, the solution is cloudy or contains visible particles, the solution should not be used.

Diffusion of botulinum toxin is about moving the molecules from the injection site, on the basis of the concentration difference of the botulinum toxin with respect to the surrounding tissue.

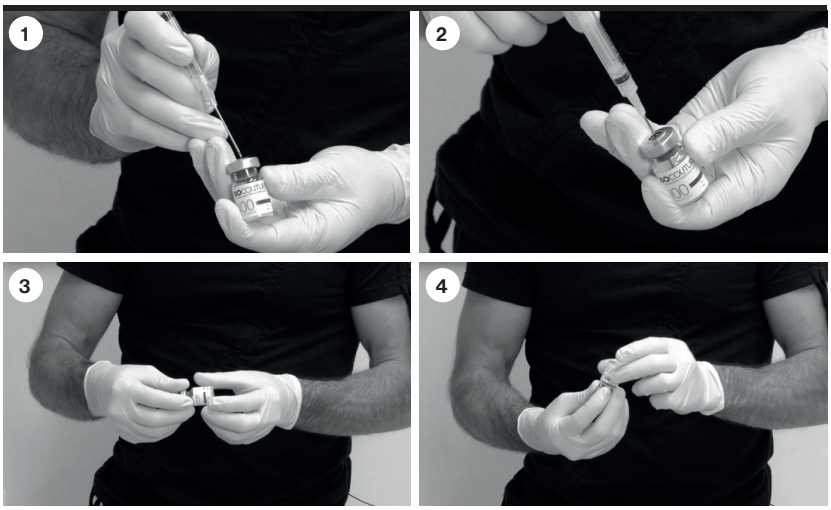


Figure 3
Reconstitution of Bocouture®

1 Fill a syringe with 2.5 mL of (bacteriostatic) saline and attach a 18G needle.
2 When the needle is advanced through the rubber cap, the vacuum inside the vial pulls the cotents of the syringe into the vial.
3 After removing the needle, swirl the saline by rolling the vial.
4 Make sure the saline touches everywhere inside the vial, including the rubber cap to assure all neurotoxin gets into the solution.

Video 2
Reconstitution of Bocouture®

Watch video at http://bit.ly/botulinum-toxin-in-aesthetic-medicine-uma-academy

1.7 Contra indications

Absolute contra indications

1 Fever or feeling sick
2 Permanent filler in the treatment area
3 Hypersensitivity to botulinum toxin type A or any product used as a component
4 Myasthenia Gravis, Eaton Lambert Syndrome or other muscle activity disorders in medical history
5 Pregnancy or lactation
6 Infection in the treatment area
7 Melanoma or other malignancy in the treatment area

Relative contra indications

1 Skin diseases or inflammation in treatment area
2 Coagulation disorders
3 The use of anti-coagulation, in association with an increased risk of bruises
4 The presence of ALS or peripheral neuromuscular disorders
5 Body Dysmorphic Disorder
6 Specific additional treatments in the treatment area, before or after the botulinum toxin treatment
7 Aminoglycoside antibiotics or drugs affecting neuromuscular transmission (for example tubocurarine-type muscle relaxants)
8 Permanent fillers around the treatment area

1.8 Patient consultation and documentation

A good understanding of the wishes of the patient is essential. The physician should create and verify realistic expectations of the possible results and complication risks. During consultation, a mirror or photographs can be used to specify the treatment areas and expected results, limitations of the botulinum toxin treatment, and pointing out pre-existing asymmetries. The types of wrinkles (dynamic, static), their etiologies and treatment options should be explained. All relevant information should be entered in the patient file. A thourough patient history must also be documented in the patient file and should include information on general health, pregnancy, lactation, allergies, use of medication and contra indications.

There are cultural differences between different patient subgroups affecting beauty ideals. European patients generally want a subtle, natural and fresh look, not necessarily a frozen or mask face appearance. The underlying reason for this is that this will improve self-confidence and overall quality of life. The treatment dose is at the discretion of the practitioner on the basis of individual anatomy and to the wishes of the patient. The abovementioned key messages should be communicated to patients and it should be documented that the patient has received this information.

1.9 Patient information

- **Mechanism of action:** Botulinum toxin causes weakening of the treated muscle. The muscle recovers fully from this temporary weakening after several months. Botulinum toxin is a protein that temporarily blocks the signal transmission between nerve and muscle.
- **Duration of effect:** The relaxation of the treated muscles starts to become noticeable after a few days and is at its maximum after about 2-4 weeks. The effect lasts about 3-4 months (by repeating the treatment, the effect may last longer when the muscle is not fully recovered from the previous treatment and the effect may last shorter if the dose is reduced).
- **Treatment repetition:** Treatment should be repeated after about 3-4 months, but not earlier due to the potential for immunogenicity to botulinum toxin in the case of Vistabel or Azzalure. Bocouture®/Xeomin® does not have an increased risk of immunogenicity and so the 3 months interval limitation is not mentioned in the instructions for use.

1.10 Complications and side effects

01

Headaches
Some patients may have headaches and flu-like symptoms for several days. These side effects are very rare.

02

Local side effects
Local side effects can be expected such as injection pain, redness, bruising and possibly a small amount of bleeding at the injection site.

03

Unintended muscle effect
An adjacent muscle can be affected unintentionally, thus an unintended aesthetic effect may occur (frontalis muscle: brow ptosis; m. levator palpebrae: levatorptosis (dropped eyelid); zygomaticus major muscle: altered smile). If there is insufficient effect, a touch-up treatment can be performed after 2 weeks.

04

Allergic reaction
Allergic reactions are very rare (less than 0.1%).

1.11 Pre and post procedure

Informed consent

A treatment agreement must meet the following characteristics:

1. Patient expressly consents to treatment and acknowledges assumption of risks.
2. It must be in writing (digital or print).
3. It has to contain the date and the signature of the patient.
4. It must be signed before the treatment.
5. Some countries adhere to a cooling-off period of 24 hours.

Photography

Photography represents an integral part of the aesthetic patient file. A patient must consent to having their image taken before being photographed. Take photos in relaxed and dynamic states, from different angles, and in a standardized manner.

Facial analysis and physical examination

During the physical examination the position of the eyebrows, the degree of dynamic wrinkles, the appearance of the skin, volume (loss), creases, folds, scars, etc. should be analyzed and discussed with the patient. Attention should be paid to potential malignant lesions (eg melanoma) and other skin pathologies that are contra indications for injection. Analysis of facial muscles should be performed in relaxed and dynamic states: while frowning, raising eyebrows and squinting. During facial analysis, pay attention to symmetry, anatomical features of the muscles and the pattern of lines and wrinkles. Based on muscular anatomy, marking of the injection points is performed immediately prior to injection with the patient positioned on the treatment chair.

Video 3
Facial assessment and anatomical background prior to botulinum toxin treatment

Watch video at http://bit.ly/botulinum-toxin-in-aesthetic-medicine-uma-academy

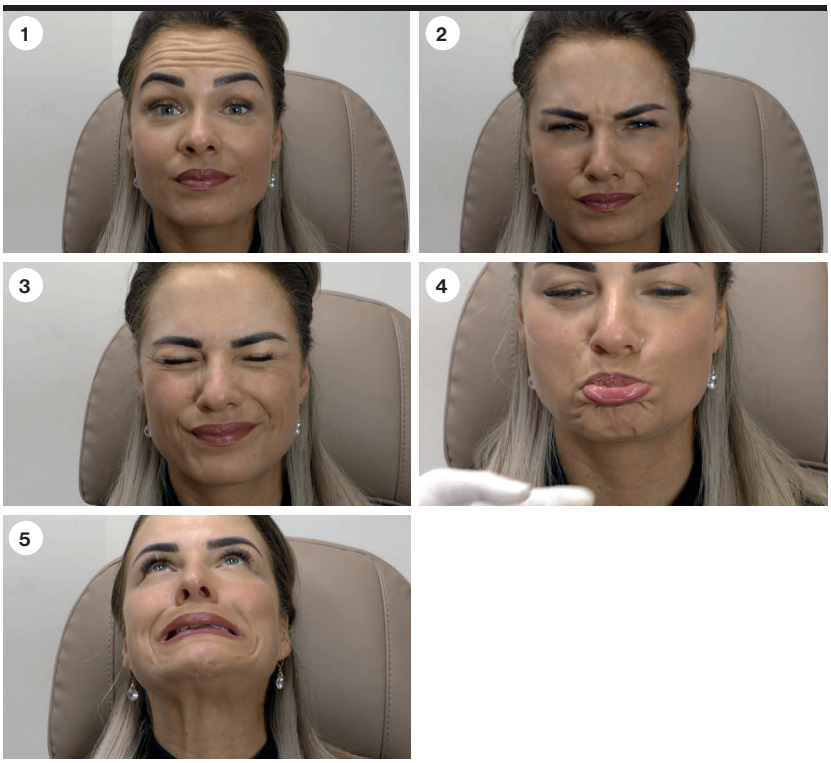


Figure 4
Facial assessment

1 Assessment of the frontalis muscle.
2 Assessment of the glabella.
3 Assessment of the orbicularis oculi muscle.
4 Assessment of the mentalis muscle.
5 Assessment of the depressor anguli oris muscle and the platysma .

Patient preparation

If required, topical creams, vibration devices or cooling can be considered for anesthesia. Position the patient in a comfortable treatment chair with proper lighting. General infection prevention measures should be used including wearing disposable gloves and disinfecting the skin prior to injection.

After care

Many experts advise their patients to properly frown and flex the treated muscles for 1 hour after treatment in order for the toxin to bind at the target receptor. However, no evidence was found to support this statement. In fact, the basic tonus of the muscle may be sufficient to allow for binding of the protein to its receptor. Patients are advised not to rub their eyes, not to touch, rub or press the injection site, have facial massages, do strenuous exercise, bend or lay down, sunbathe, visit a sauna, or consume alcohol for several hours after the treatment, in order to minimize spread. This well-meant advice is not evidence-based, but no harm is done when advising patients of this after care.

1.12 General injection techniques

The following injection techniques are generally used for botulinum toxin treatment:

01

Intramuscular bolus technique

With this widely-used technique the point of the needle is placed directly through the skin into the muscle at a location where a high concentration of motor endplates is presumed to be present. The needle tip is not displaced while the botulinum toxin is injected.

02

Subcutaneous bolus injection technique

This technique is used when the risk of passing through a superficial muscle needs to be minimized, for example in the platysma muscle

03

Intradermal bolus injection technique

This technique is used when the risk for an underlying blood vessel or diffusion radius needs to be minimized, for example in the forehead.

04

Retrograde injection technique

This technique is used when spread must be controlled, for example in the mentalis muscle, the orbicularis oris muscle, or the orbicularis oculi muscle.

05

Microtoxin injection technique

This technique is often used with hyperdiluted botulinum toxin; when the dose has to be very low and superficial, for example in the risorius muscle, forehead and lateral cheeks.

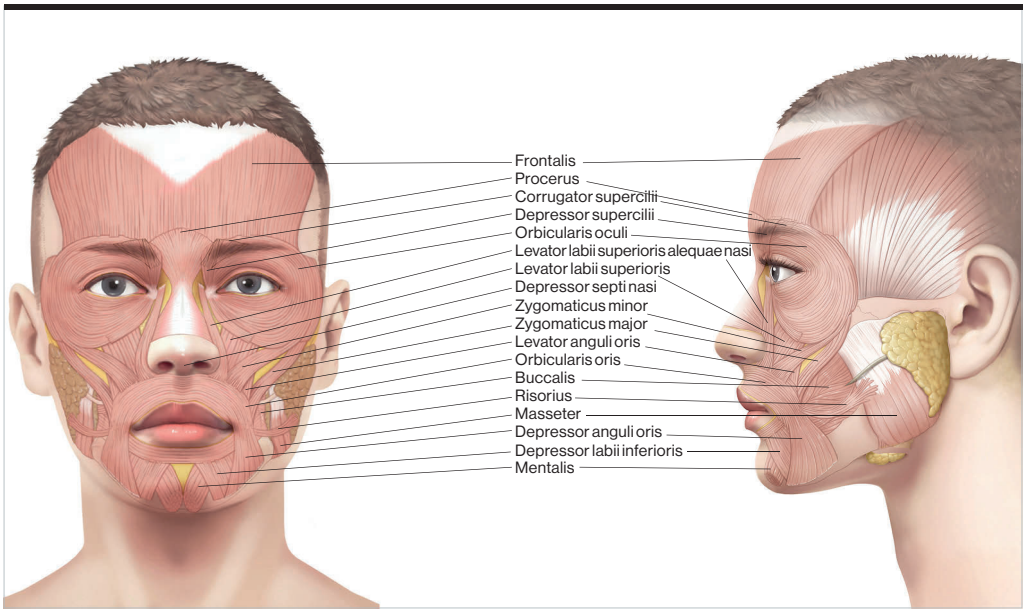


Figure 5
Facial muscles

02
upper third of the face

introduction

Muscles of facial expression maintain a balance of the mimetic movements in the face. In the upper third of the face, there are two types of muscles: levators and depressors. The frontalis muscle is the only levator for the eyebrows, while the procerus,

corrugator supercillii, depressor supercillii and the orbicularis oculi muscles are the depressors. This chapter describes the treatment protocols for each of the abovementioned muscles, respecting the balance of the eyebrows.

upper third of the face

2.1 Horizontal forehead lines (frontalis muscle)

The injection pattern of the frontalis muscle is shown in figure below. Generally, 4 to 6 injections are administered with 2 U / 5 sU per injection site at a depth of approximately 2-3 mm using an intramuscular, subcutaneous or intradermal injection technique. The first injection site can be marked at 3-4 cm cranial to the orbital rim, from the peak of the brow along the direction of the muscle fibers. The second point is found vertically from the medial canthus, at about 3-4 cm above the orbital rim. The third injection site is found between the first two points, also 3-4 cm above the orbital rim. Besides these three injection points per side, micro intradermal injections can be performed with approximately 0.5 U / 1.25 sU per microinjection to prevent any residual horizontal wrinkles.

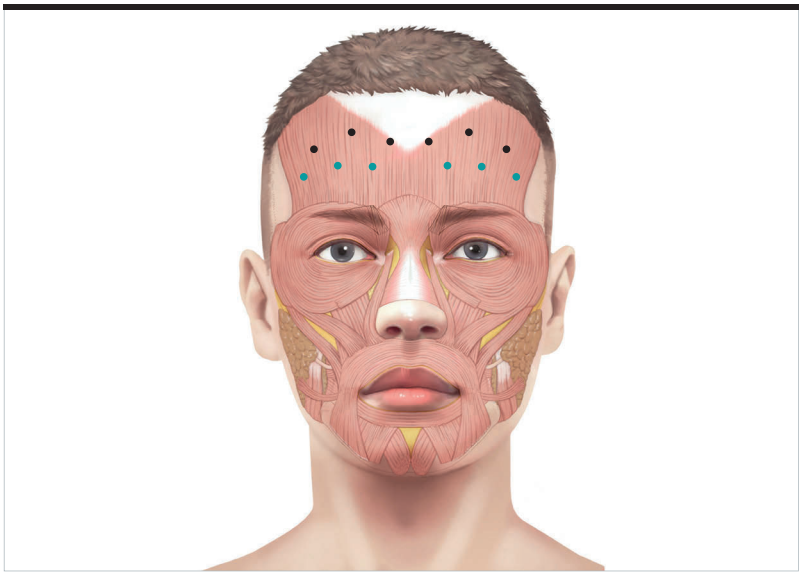


Figure 6
Injections horizontal forehead lines (frontalis muscle)

Black: the most common sites of injection (subcutaneous bolus injection technique) of about 2 U / 5 sU per injection site;
Blue: additional possible injection sites (intradermal injection technique) of about 0.5-1 U / 1.25 sU per injection site.

> As the frontalis muscle is the only levator muscle of the eyebrows, a relative overdose can result in a brow ptosis. To prevent brow ptosis, injections in the lower half of the frontalis muscle should be avoided.

Dosage frontal dynamic wrinkles
The dosage for men is different from the dosage for women with men generally receiving a higher dosage due to larger muscle development.

	Dose	Number of injection sites
Men	6-20 U / 20-60 sU	4-12
Women	6-16 U / 20-60 sU	4-12

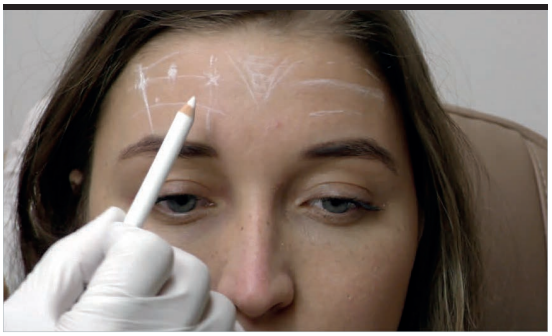


Figure 7
Horizontal forehead lines

Intramascular as well as intradermal botulinum toxin injections

Video 4
Horizontal forehead lines standard protocol

Watch video at http://bit.ly/botulinum-toxin-in-aesthetic-medicine-uma-academy

2.2 Personal tweaks with Bocouture® / Xeomin®

Having adapted the new insights of fibroblast contraction, we hyperdilute Xeomin® to approximately 6 ml saline / 100 U. When using 10 U for the forehead, (0.25 ml), we add 0.35 ml, to get a volume of 0.6 ml per 10 U. This gives most significant fibroblast contraction and may result in increased lift. The injections are performed intradermally and also have an effect on the frontalis muscle. The dose and injection points remain the same, or more points can be added to assure a homogeneous distribution of the product. If needed, the dose can be increased in the upper forehead at follow-up visits to further reduce muscle strength.

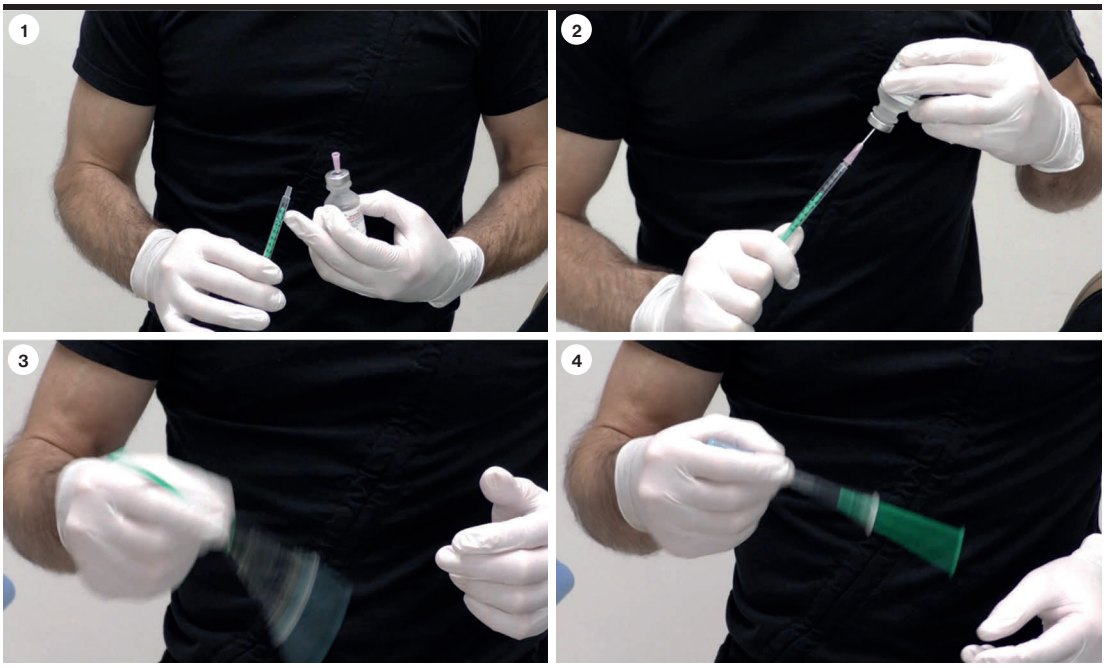


Figure 8
Hyperdiluting Bocouture®/Xeomin®

1 In this case, 12 U for the forehead was chosen.
2 The ideal dose is 6 ml / 100 U = 0,72 ml / 12 U, so add saline until approximately 0,7 ml.
3 Leaving an air bubble in the syringe, gently centrifuge the bubble to the other side.
4 Repeat a few times for homogeneous solution.

upper third of the face

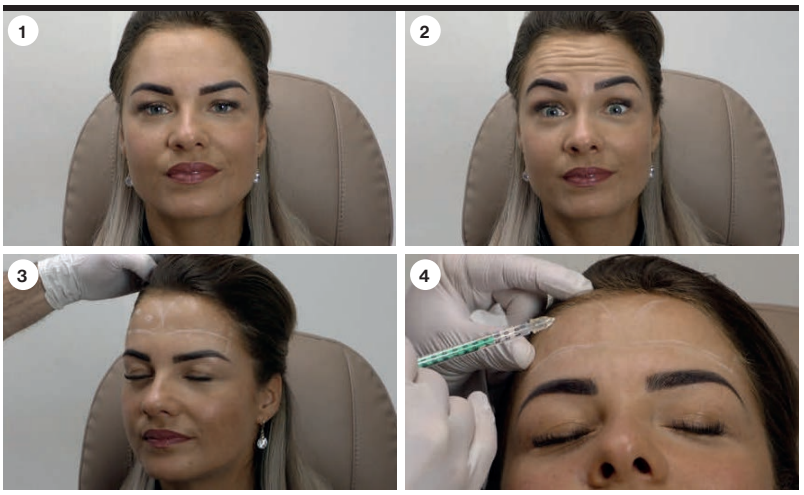


Figure 9
Intradermal injection of hyperdiluted botulinum toxin

1 Frontalis muscle in relaxed states.
2 Frontalis muscle in contracted states.
3 Marking each marked point, in this case hyper diluted Bocouture® (100 U / 6 ml).
4 Injecting each marked point, in this case hyper diluted Bocouture® (100 U / 6 ml).

Video 5
Intradermal injection of hyperdiluted botulinum toxin

Watch video at http://bit.ly/botulinum-toxin-in-aesthetic-medicine-uma-academy

2.3 GRID21 and Grid ONE21 methods

A relatively new bespoke treatment option is using the GRID21 method. This is an individualized treatment approach for the frontalis muscle designed by Dr. Phillip Levy where the muscles are injected in up to 21 points with varying dosages in every point depending on muscular strength at those points and the desired eyebrow shape. An alternative, but similar, approach of the GRID21 method, is the ONE21 technique, developed by Dr. Carla de Sanctis Pecora et. al. It is a safe technique for the treatment of forehead wrinkles with a predictable eyebrow reshape. This protocol considers both clinical as well as anatomical patterns shown by the patient. Pre-treatment assessment of the upper face, grading of wrinkles, muscle strength, and patient request for eyebrow shape and positioning will determine the dosage for each injection points.

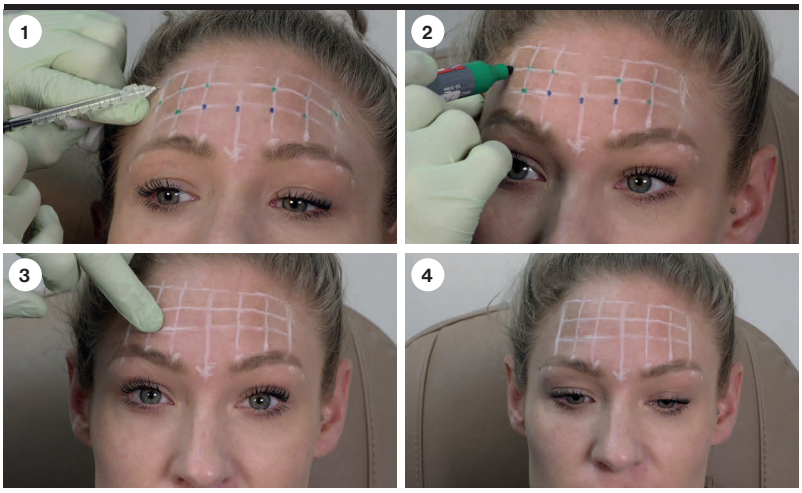
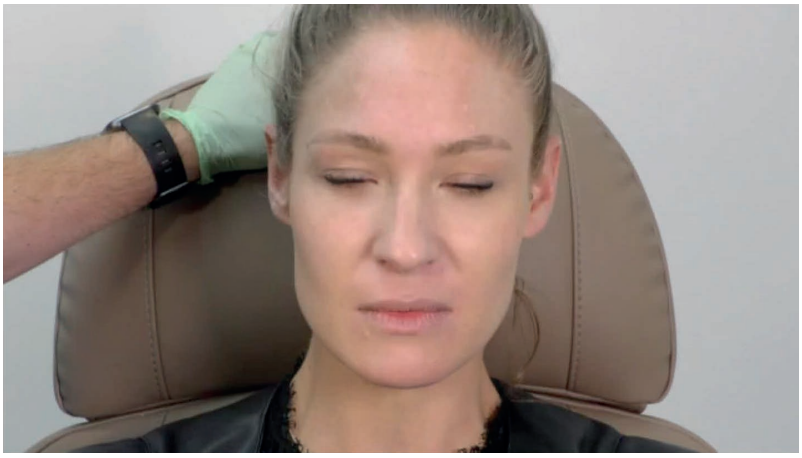


Figure 10
GRID21 method and ONE21 technique

Each point is marked with a specific dose depending on the individual muscular strength in 21 points on the forehead.

1. Marking of the grid: midline, medial canthus, mid-pupillary line, lateral canthus (vertical) and the lowest wrinkle ("Inferior Limit Line"), the highest wrinkle and a line in between (horizontal).
2. Feeling per individual intersection point the strength of the muscle.
3. By applying low, intermediate and high pressure on each individual grid point with the finger tips, the corresponding effect on the brow position can be assessed. Then, marking with corresponding colors for low, intermediate or high dose can be done per injection point.
4. Performing the injections. In this example, red = 2 U, blue = 1 U and green = 0.5 U.



Watch video at http://bit.ly/botulinum-toxin-in-aesthetic-medicine-uma-academy

Video 6
GRID21 method and ONE21 technique

upper third of the face

Complications

01

Brow ptosis

As the frontalis muscle is the only levator muscle of the eyebrows, a relative overdose can result in a lower position of the brows. The recommendation is therefore to inject the depressors of the brow in the same treatment session: procerus, depressor supercilii, orbicularis oculi and corrugator supercilii muscles. To prevent brow ptosis, injections in the lower half of the frontalis muscle should be avoided. Superficial injection is also advisable. When botulinum toxin enters into the subgaleal glide space it may easily spread caudally. Inside the muscle there are many blood vessels. If the needle punctures the vessel wall and blood flows into the surrounding tissue, more spread can be expected. Treatment of brow ptosis consists of weakening the depressors (see 'brow lift').

02

Hematoma / ecchymosis

The temporal, supraorbital and supratrochlear arteries and their branches run through the treatment area, as well as small and large veins. Good inspection is therefore important to prevent hematomas. Injecting intradermally reduces the risk of puncturing blood vessels.

03

Mephisto look

The Mephisto look, also known as the Jack Nicholson eyebrow, is characterized by medial depression and lateral elevation of the eyebrow. The cause is a reactive hyper-contraction of the lateral part of the frontalis muscle by relaxation of the medial part of the frontalis muscle. Treatment consists of the injection of 1-2 U / 2.5-5 sU in the fibers of the lateral frontalis muscle.

2.4 Glabella (various muscles)

The muscles that have an effect on the glabellar frown lines are the procerus, the depressor supercilii, the corrugator supercilii and the orbicularis oculi. Procerus: 4-6 U / 10-15 sU is injected in the midline at the level of the superciliary line, where the needle is placed perpendicular to the skin, approximately 6 mm deep (a half-needle). The two depressor supercilii muscles are both treated due to the diffusion radius of about 1 cm at this dosage.
The medial injection of the corrugator supercilii muscle, about 0.5 cm above the base of the eyebrow (at the level of the medial canthus), is given deep at about 8 mm (¾ needle) due to the medially located origin at the periosteum 4-6 U / 10-15 sU. The lateral injection site is superficial 2-4 mm deep (¼ needle), directly medial to the skin insertion. The insertion of the corrugator can be found by asking the patient to frown. A depression in the skin (corrugator dimple) marks the place where the muscle fibers pull the skin towards the medial origin. The corrugator is injected 0.5-1 cm outside the orbital rim to avoid brow ptosis and eyelid ptosis.

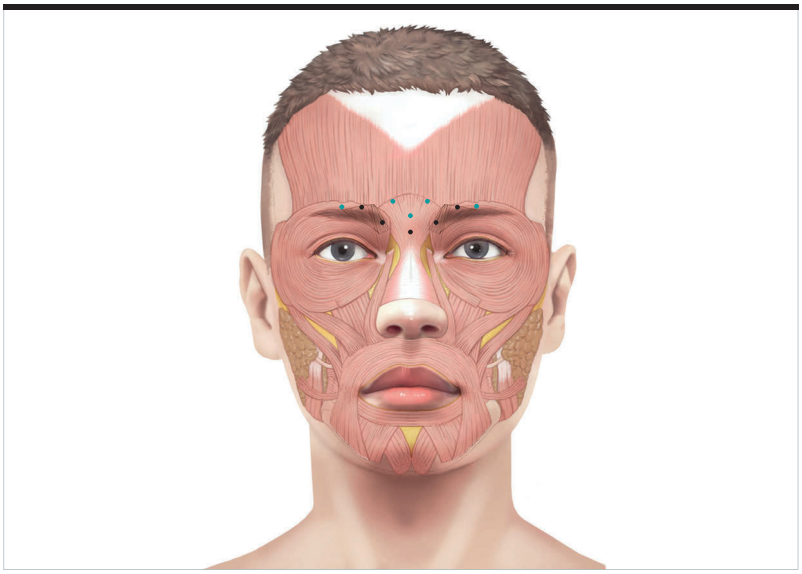


Figure 11
Injections pattern of the glabella

Black: the most common sites of injection (intramuscular injection technique);
Blue: additional possible injection sites (lateral: intradermal technique, be careful of brow ptosis; medial: intramuscular technique).

Dosage Glabella
The dosage for men differs from the dosage for women with men generally receiving a higher dose due to larger muscle development. With men, the corrugator supercilii muscle often runs more laterally.

	Dose	Number of injection sites
Men	24 U / 60 sU	5-7
Women	24 U / 50 sU	5-7

upper third of the face

High dose glabella treatment

Building up to the introduction of a new botulinum toxin product on the US market, A recent study showed a positive dose-response relationship with increasing doses of IncobotulinumtoxinA (INCO, Xeomin/Bocouture) for the glabellar frown lines (GFL). This study demonstrated a median duration of effect of 185 days with a dose of 50U INCO and 210 days with 75U INCO. The primary efficacy endpoint was duration of effect was defined as at least one point improvement compared to baseline using the Facial Wrinkle Scale.[61]

It is hypothesized, based on preclinical data, that a higher dose results in a longer duration of effect because more botulinum toxin can bind to the motor endplates, and, with that, more light chain molecules to reach the cytosol of the neuron.[62] Consequently, the degradation will take longer.[63]

Other commercially available botulinum toxin, such as OnabotulinumtoxinA and AbobotulinumtoxinA, have showed similar positive dose-response curves for the treatment of GFL.

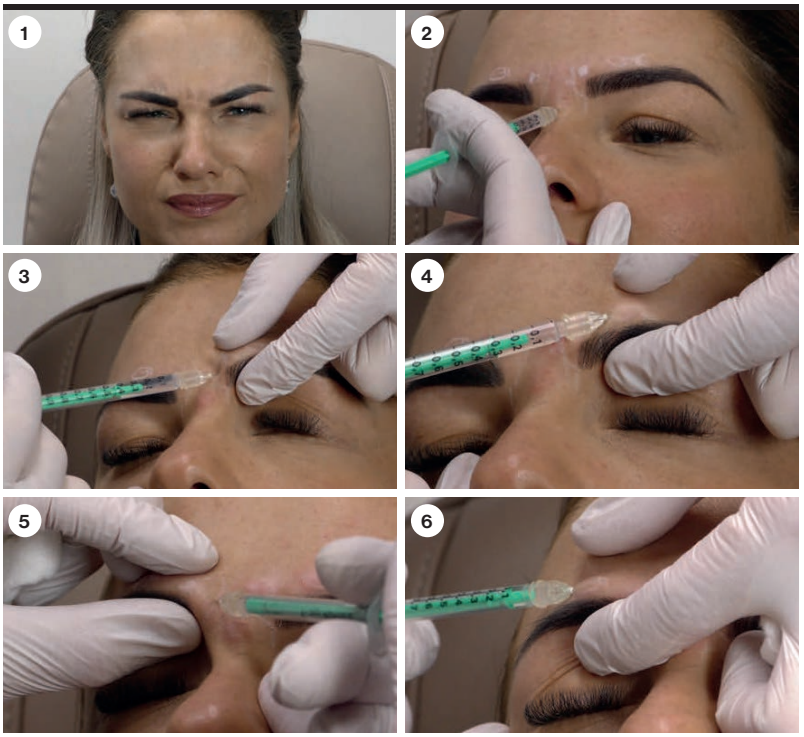


Figure 12
Glabella injections

1 Glabellar complex in contracted state.
2 Markings and procerus muscle injection.
3 and **5** Deep injection in the medial side of the corrugator supercilii muscle.
4 and **6** Superficial injection in the lateral side of the corrugator.

Video 7
Glabella injections

Watch video at http://bit.ly/botulinum-toxin-in-aesthetic-medicine-uma-academy

Complications

01

Mephisto look

The mephisto look is characterized by medial depression and lateral elevation of the eyebrow. The cause is a reactive hyper-contraction of the lateral part of the frontalis muscle by relaxation of the medial part of the frontalis muscle. This is caused by injecting too cranial to the corrugator supercilii muscle resulting in the frontalis muscle being treated as well. It can be avoided by injecting deep into the medial head with a superficial injection in the lateral part of the corrugator supercilii muscle. Corrective treatment requires injection of 1-2 U / 2.5-5 sU in the fibers of the lateral frontalis muscle.

02

Blepharoptosis or levatorptosis

When botulinum toxin enters the intra-orbital space it can reach and weaken the levator palpebrae muscle, causing levator ptosis. The cause of levator ptosis is anatomical in nature; the orbicularis retaining ligament is impermeable to fluid and thereby prevents diffusion or spread to the intra-orbit. However, at the location of the supraorbital notch/foramen an opening exists in this ligament, through which the botulinum toxin can pass. Prevention therefore consists of respecting the distance (0.5-1 cm) from the orbital rim and, in particular, the avoidance of a deep injection near the supraorbital foramen. Treatment includes prescribing eye drops 0.5% apraclonidine three times daily in the affected eye for a maximum of 1 month. Apraclonidine is an agent that is normally intended to reduce the intraocular pressure in case of glaucoma. A side effect of this drug is the effect desired by ptosis: the Müller muscles contract which raise the eyelid 1-3 mm.

03

Brow ptosis

When the lower part of the frontalis muscle is unintentionally weakened, the eyebrow may drop. When injecting the lateral part of the corrugator, the best option is to inject from lateral to medial. In order to prevent brow ptosis, the most lateral border of the corrugator supercilii muscle should be the midpupillary line. Should this complication occur, the depressor muscles can be treated: the orbicularis oculi and lateral corrugator supercilii muscles.

04

Hematoma

The supraorbital and supratrochlear arteries and their branches run through the treatment area, as well as small and large veins. Good inspection is therefore important to prevent hematomas. Intradermal injection reduces the risk of puncturing blood vessels.

upper third of the face

2.5 Periorbital wrinkles (orbicularis oculi muscle)

The orbicularis oculi is treated with 3-4 injections of 2-4 U / 5-10 U per injection site. The injection depth is superficial, approximately 2-3 mm (¼ needle) deep, and the pattern is radial, about 1 cm from the orbital rim. Due to the proximity of the bilateral venous plexus, there is a risk of hematomas and the skin needs to be inspected for the course of superficial veins. Cranially, the area of the medial temporal crest should be avoided to prevent influencing the frontalis muscle, and caudally, deep injections should be avoided to prevent influencing the zygomaticus major muscle. Additional intradermal microinjections can be given to treat the finer infraorbital lines.

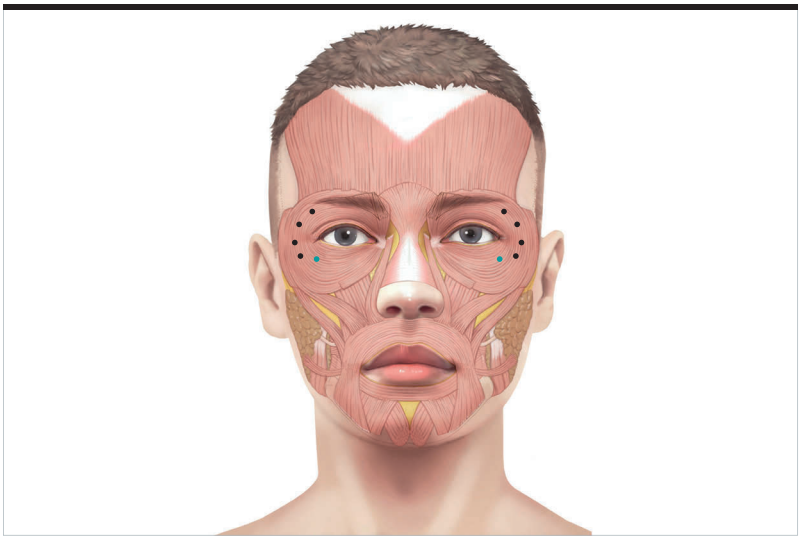


Figure 13
Injection pattern for dynamic periorbital wrinkles

Black: the most common sites of injection (intramuscular injection technique);
Blue: additional possible injection sites (intradermal technique).

Dosage orbicularis oculi muscle
The dosage for men is generally higher than for women due to larger muscle development.

	Average dose	Number of injection sites
Men	20-30 U / 20-60 sU	3-6 per eye
Women	10-30 U / 20-60 sU	3-6 per eye

Complications

01

Brow ptosis

When botulinum toxin is injected too cranially, the caudal area of the frontalis muscle can be affected. As a result, this eyebrow levator muscle will relax and the lateral eyebrow may be lowered. This complication can be avoided by choosing a lateral injection site closer to the brow. Should it occur, the complication can be treated by injecting the orbicularis oculi muscle at the temporal crest.

02

Diplopia

When the needle is inserted through the orbicularis retaining ligament, botulinum toxin can diffuse to the intraorbital muscles that control eye movements causing diplopia. To prevent this complication, it is recommended to keep a minimum distance of 1 cm from the orbital rim.

03

Drooping mouth

If botulinum toxin affects the zygomaticus major muscle (or in extremely rare cases the zygomaticus minor muscle), this will affect the position of the oral commissure. The zygomaticus major muscle has its origin in the periosteum of the zygomatic bone and therefore deep to the orbicularis oculi muscle. Prevention is by avoiding deep injections in this area. Treatment consists of relaxing the antagonist, which is the depressor anguli oris muscle.

04

Hematoma

The venous plexuses in the orbital area pose a significant risk for hematoma. Proper inspection of the skin with a good examination lamp is essential. Treatment consists of direct compression.

05

Eye bags

When the lower eyelids are treated, the tonus of the orbicularis oculi muscle might be weakened in such a way that it bulges anteriorly due to pressure of the underlying fat. To prevent this complication, the dose of toxin for the lower eyelids should be limited to a maximum of 1 U / 2.5 sU per injection site.

Infraorbital bags may also occur as a result of lymphatic stasis causing edema. The orbicularis oculi muscle has a pumping function for the drainage of lymphatic fluid. When this pump is weakened by toxin, stasis and accumulation of lymphatic fluid may result. To prevent this occurring minimal dosage should be used. This side effect is self-limiting and usually disappears within 2 weeks as the lymphatic system will adjust to the new circumstances. Manual lymphatic drainage can also help disperse the fluid.

upper third of the face

2.6 Brow Lift (various muscles)

The brow depressors are all treated at the level of the eyebrow. In addition to the standard glabella injection sites, treatment includes two lateral injections in the orbicularis oculi muscle of about 2-4 U / 5-10 sU each. The lateral injections should not be administered above the level of the eyebrow to avoid influencing the frontalis muscle.

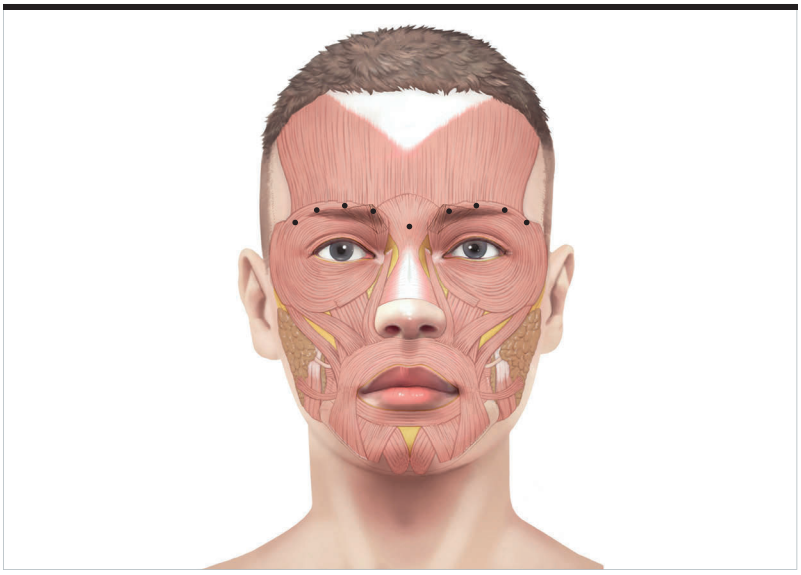


Figure 14
Injection pattern for brow lift

Toxin is administered at 2-4 U / 5-10 sU per injection site (intramuscular injection technique) and injected directly into or caudal to the eyebrow laterally and into or just cranial to the eyebrow medially in combination with procerus injection.

2.7 Tension headache and migraine

Targeting the glabella, frontalis and/or orbicularis oculi muscles in combination with the temporalis muscle is often effective for the treatment of tension headache. The temporalis muscle can be treated by four injections and a total of 16-32 U / 40-80 sU per side, with the injection points about 2-3 cm apart. Injections should be deep as the temporalis muscle lies just above the periosteum, underneath the deep temporal fascia (temporalis muscle aponeurosis). Palpate before treatment to locate the superficial temporal artery. In some individuals the masseter muscle may also contribute to headaches. Injection of this muscle is described in the section on masseter hypertrophy. Finally, in some patients, the trapezius and occipitalis muscles may contribute to tension headaches and migraines. However, treatment of these muscles is beyond the scope of these protocols. The temporalis muscle is often hypertrophic in patients with tension headaches and migraines. Therefore, treatment of this primarily medical condition has an aesthetic goal as well and is therefore included in this book.

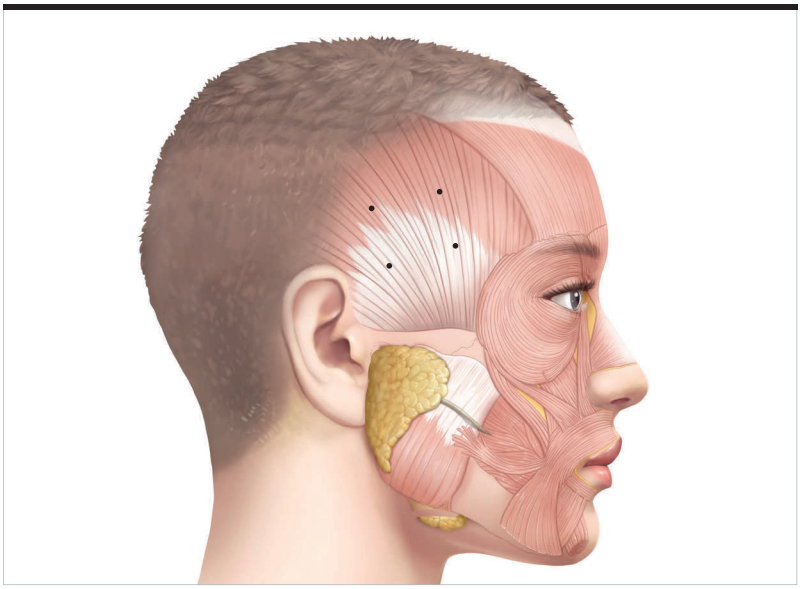


Figure 15
Injection technique for the temporalis muscle for treatment of migraine

Inject the temporalis muscle with an intramuscular bolus technique using 4-8 U / 10-20 sU per injectio and spacing injection points approximately 2-3 cm apart.

Complications

01

Skeletonized appearance
A side effect of temporalis muscle injection with toxin can be a reduction in volume of the muscle, leading to a skeletonized appearance. Treatment consists of injecting volumizing fillers in the temporal area.

02

Hematoma
A number of arteries are found in the temporal area, including the superficial temporal artery, middle and deep temporal arteries, and periorbital venous plexuses. Avoidance can be improved by palpation. If an artery is inadvertently punctured, direct compression should be continued for at least 2 minutes in case of arterial puncture and 1 minute in case of venous puncture.

upper third of the face

2.8 Lower eyelid wrinkles and widening of the eyes (orbicularis oculi muscle)

Injections must be placed very superficially and at a very low dose (0.5-1 U / 1.25-2.5 sU per injection, subcutaneously). In addition, hypertrophy of the pretarsal orbicularis oculi can be treated. 1-2 U lateral to the midpupillary line 1-2 mm below the lashes.

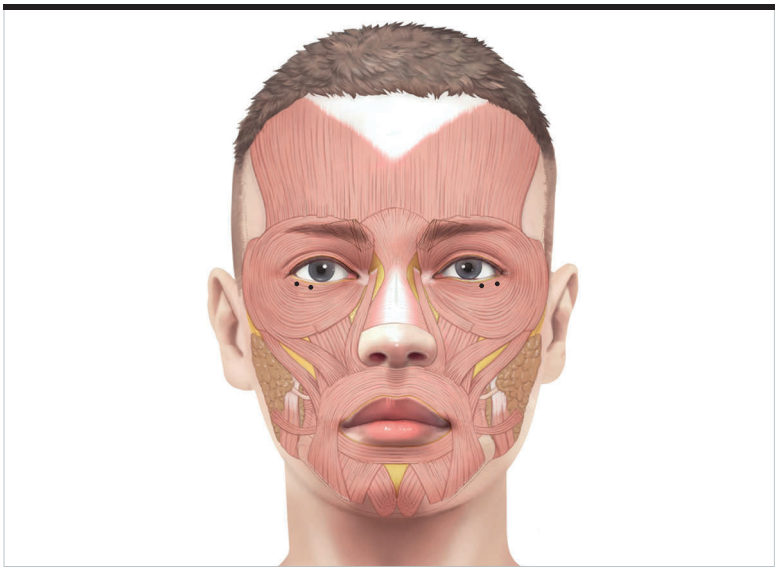


Figure 16
Injection pattern for treatment of the orbicularis oculi muscle

Toxin is administered at 1-2 injection points in the ramus tarsalis, 2-3 mm below the lashes with subcutaneous injection of 0.5-1U / sU 1.25-2.5 per injection point. Injections are lateral to the midpupilliary line.

Figure 17 and Video 8
Lower eyelid wrinkles and widening of the eyes (orbicularis oculi muscle)

Two drops of 0.5U / 1.25 sU are injected subcutaneously in the lower eyelid while the patient is asked to look up.

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Complications

01

Ectropion
Lower eyelid injection sites medial to the lateral canthus are associated with a higher risk of causing ectropion. Eyelid laxity must be tested prior to treatment by a snap test, which involves pulled down the lower eyelid with a finger and releasing. The eyelid should reposition (snap) quickly (within a second). A slow snap test indicates an increased risk for ectropion.

02

Eye bags
When the lower eyelids are treated, the tonus of the orbicularis oculi muscle may be weakened in such a way that it bulges anteriorly due to pressure of the underlying fat. To prevent this complication, the toxin dose for the lower eyelids should be limited to a maximum of 1 U / 2.5 sU per injection site. Infraorbital bags may also be caused by lymphatic stasis. The orbicularis oculi muscle has a pumping function for the drainage of lymphatic fluid. When this pump is weakened, stasis and accumulation of lymphatic fluid may result. This side effect can be prevented by minimizing the dose of toxin. It is self-limiting and usually disappears within 2 weeks as the lymphatic system adjusts to the new circumstances. Manual lymphatic drainage can help disperse the fluid.

03
middle third of the face

introduction

Although the use of botulinum toxin is mainly indicated in the upper third of the face, there are several indications for the middle third of the face. These injections are more subtle and require more experience as an injector.

Proper knowledge of the anatomy and physiology of muscles is required. Especially around the modiolus, which has a complex equilibrium of agonistic and antagonistic actions of multiple

muscles. Excessive or inappropriate injections lead to undesirable side effects. Adhering to the correct treatment protocols can lead to highly satisfying results, reducing bunny lines and peri-oral lines, correction of a gummy smile, and facial asymmetries.

middle third of the face

3.1 Bunny lines (LLSAN and depressor supercilii muscles)

Nasal rhytides or bunny lines can be treated by injecting 2-4 U / 5-10 sU of toxin at a depth of 2-4 mm, just above the center of the levator labii superioris aleque nasii muscle (LLSAN), and just medial to the vertical line between ala and medial canthus. At this position the muscle can be easily palpated during contraction. Concurrent treatment of the depressor supercilii muscle is sometimes also necessary in which case both sides should be injected with about 1-2 U / 2.5-5 sU at a depth of 1-2 mm injection pattern for nasal rhytides (bunny lines).

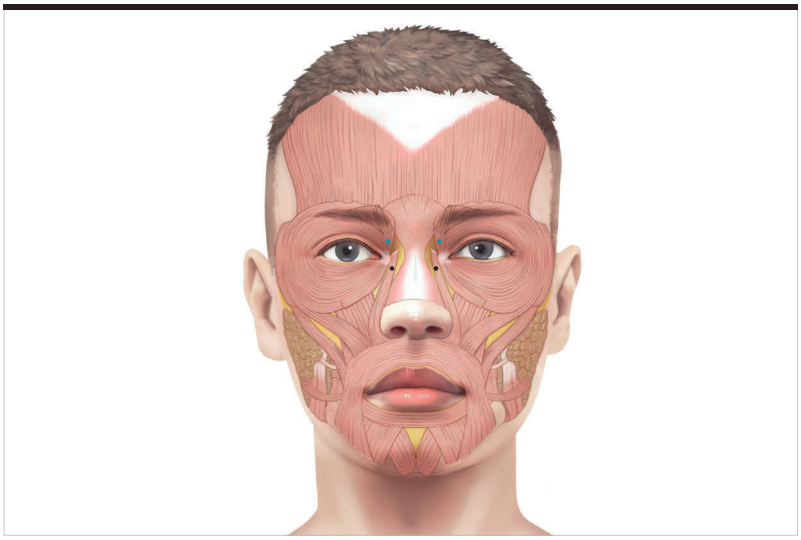
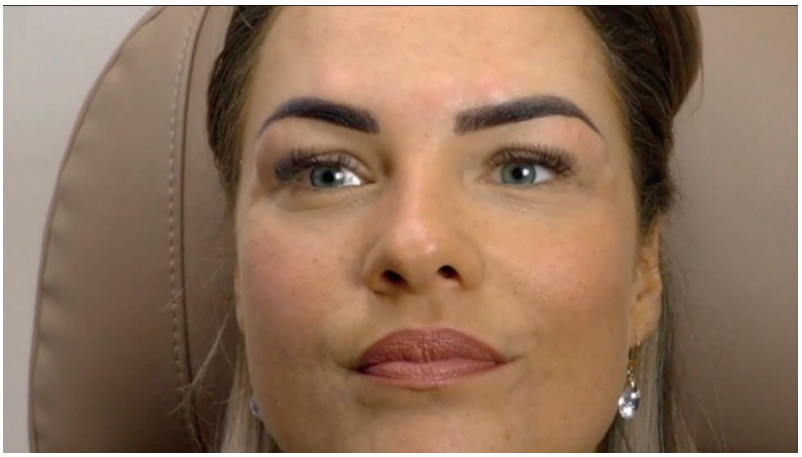


Figure 18
Injection pattern for nasal rhytides (bunny lines)

Black: the most common sites of injection (intramuscular injection technique) uses 2-4 U / 5-10 sU at an injection depth of 2-4 mm;
Blue: additional potential sites of injection intramuscularly 1-2 U / 2.5-5 sU, at a depth of 2-4 mm.

Figure 19
Bunny lines

1 Contract state
2 Markings and injection



Watch video at http://bit.ly/botulinum-toxin-in-aesthetic-medicine-uma-academy

Video 9

Bunny lines

1. Glabellar complex in contracted state.
2. Markings and procerus muscle injection.
3. Deep injection in the medial side of the corrugator supercilii muscle.
4. Superficial injectio in the lateral side of the corrugator.

Complications

01

Altered smile

Injecting in the lower part of the LLSAN may lead to lowering of the upper lip and less visible teeth display when laughing. In order to prevent this side effect, inject cranial to the middle of the muscle, between the ala and medial canthus.

02

Diplopia

Unintentional treatment of the intraorbital muscles is a theoretical possibility with injection of the depressor supercilii muscle. Taking into account the diffusion radius, this complication can be prevented by keeping a distance of approximately 1 cm from the orbital rim.

03

Hematoma

The angular artery runs very close to the LLSAN. It is therefore wise to inspect the area well, as the artery is located subcutaneously. Care must also be taken with superior injection as the a. angularis runs close to the caudal insertion of the depressor supercilii muscle.