CONTENT

Fig. 5.4 The total-face approach injection sites. Injection sites to treat the glabellar region (A), eyebrows (B), mephisto (C), lateral canthal lines (D), forehead (E), lower eyelid (F), open eye (G), bunny lines (H), gummy smile (I), upper and lower lip (J), marionette lines (K), mentalis (L), and platysma (M). (The facial illustrations are reproduced from Sattler, G., et al. [2009]. *Bildatlas der ästhetischen Botulinumtoxin-Therapie*. KVM Verlag with permission from KVM Verlag. Injection schemes are reproduced from Imhof, M., Podda, M., & Sommer, B. [2018]. *Guidelines aesthetic botulinum toxin therapy with permission from German Society of Dermatology*. German Society for Dermatosurgery, German Society for Dermatology.)

with the vacuum-dried product, significantly decreasing the protein load by employing a vacuum-drying process also seemed to confer immunological benefits. Specifically, of the 1087 treatments administered with the freeze-dried product, two cases of antibody formation were observed because of exposure to that product whereas, no cases were observed following any of the 2231 treatments administered with the final FDA-approved commercial vacuum-dried product.

CLINICAL

Evolus, Inc. undertook the clinical development of prabotulinum toxin A for the treatment of glabellar lines in Western markets, including one head-to-head Phase III comparison with onabotulinum toxin A (BOTOX Cosmetic, Allergan, Irvine, CA). Early studies for this indication, which also included one head-to-head comparison with onabotulinum toxin A, were undertaken in South Korea, as were two additional head-to-head comparisons for other indications—one in crow's feet, the other in post-stroke upper limb spasticity.

Clinical Studies in the US, UK, EU, and Canada for Glabellar Lines

In 2014, Evolus initiated a comprehensive five-study prabotulinum toxin A clinical development program in the US, EU, UK, and Canada to meet the various regulatory requirements needed to obtain marketing approval for the treatment of moderate to severe glabellar lines. The program included three 150-day, multicenter, randomized, double-blinded, controlled, single-dose Phase III efficacy and safety studies. Of these, two (EV-001 and EV-002) were placebo-controlled pivotal studies conducted in the US that adhered to FDA guidance on developing botulinum toxins for this indication; the other (EVB-003) was a placebo- and active-controlled study conducted in the EU, UK and Canada. In addition, there were two 1-year, open-label, repeat-dose, long-term Phase II safety studies (EV-004 and EV-006). In total, 2116 subjects were enrolled.

In these studies, subjects received intramuscular injections of 0.1 mL in five target sites in muscles known to contribute to the formation of glabellar lines. Prabotulinum toxin A-treated subjects received a total of 20 U per

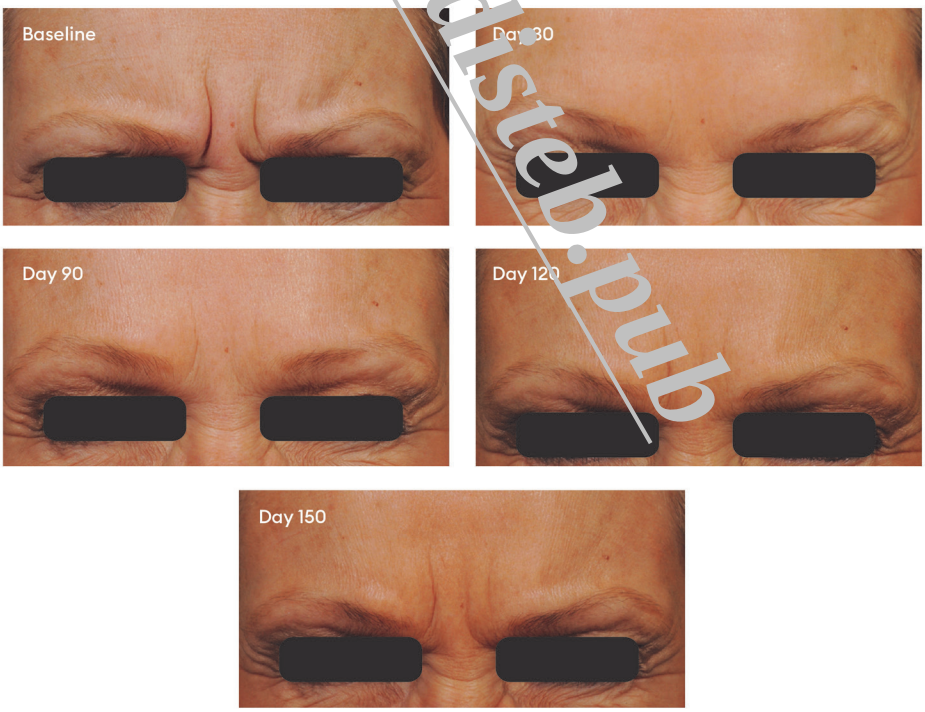

Fig. 6.1 Glabellar lines at maximum frown at baseline, and at days 30, 90, 120 and 150 following treatment with 20 U prabotulinum toxin A. *(Reprinted with permission from Wolters Kluwer Health Inc.)*

Further studies at higher doses are recommended to determine optimal dosing of Myobloc, without compromising its safety profile.

TREATMENT CONSIDERATIONS FOR MYOBLOC

Previous studies have been used as a basis to establish initial approximates for effective doses of Myobloc in the treatment of facial rhytids (Table 7.2).

The procerus complex and corrugators supercilii muscles are treated to eradicate glabellar lines. A dose totaling 20 to 30 U of BTX-A is divided and equally injected into five sites compared to the Myobloc treatment, which requires 2000 to 3000 U divided among only four injection sites resulting in comparable results. The injection of the frontalis utilizes 15 to 30 U of BTX-A distributed evenly over 5 to 6 injection sites and provides satisfactory results while the Myobloc in quantities of 1000 to 2500 U per side yields similar results as well. To achieve effective results in the lifting of the brow, injections of 1500 U are directed to the corrugator supercilii, the procerus complex and the medial portion of the orbicularis oculi muscle. For the treatment of crow's feet injecting 10 to 15 U of BTX-A divided into two to three sites per side yields similar results as employing 1000 to 1500 U per side of Myobloc, while diffusion characteristics of Myobloc taken into consideration in this scenario (Fig. 7.1).

ADVERSE EVENTS

Complication profiles for BTX-A versus Myobloc are quite similar with temporary mild bruising and headaches. In the rare occurrence, potential complications include eyelid and brow ptosis, and asymmetric brow elevation. It is imperative to see a fully qualified and skilled physician with thorough understanding of injection points and dosages for optimal results and minimal complications.

TABLE 7.2 **Provisional Dosing Guidelines for Botulinum Toxin B Injections for Facial Rhytids**

	BTX-B (MYOBLOC®)	
Muscle Site	**Units**	**No. of Injections**
Glabella	2000–3000	3
Frontalis	1000–2500	3–6
Brow lift	300–500 per side	1 per side
Periorbital	1000–1500 per side	1–2 per side

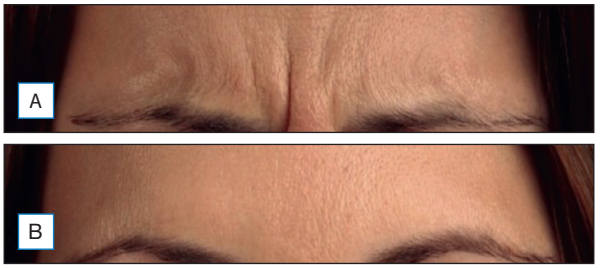

Fig. 7.1 Patient frowning (**A**) before, and (**B**) 12 weeks after treatment with 3000 U of botulinum toxin type B to the glabella.

CONCLUSIONS

In recent years, there has been a strong surge in demand from patients for safe and effective aesthetic solutions to combat signs of aging manifested by the formation of facial rhytids in the glabellar, forehead, and periorbital regions. The overactive nature of the underlying facial muscles has been successfully treated by botulinum toxins, which weaken the muscles and cause paralysis, and are particularly effective for patients with prominent hyperfunctional facial lines. BTX-A and Myobloc are two serotype formulations of botulinum toxin that are available in the United States. Each has its own unique mechanism of action, binds serotype-specific receptors, and targets specific intracellular proteins. Myobloc comes as a ready-to-use liquid formulation compared to the BTX-A, which is found in stable powder form requiring reconstitution before injecting. Although both toxins can elicit an immune response, further clinical studies are needed to demonstrate with toxin is more prone to provoke an immune response. BTX-A has been used in aesthetic medicine for several years, with numerous clinical studies substantiating its efficacy, whereas Myobloc has only fairly recently been used for aesthetic indications. Nevertheless, initial findings on Myobloc indicate that it can deliver more rapid and greater results in paralyzing muscles. The safety profile of Myobloc and BTX-A is favorable, and the likelihood of serious adverse effects is low; albeit both toxins are highly potent and extreme care should be taken,

Fig. 9.1 Product package of Neuronox®, Innotox®, and Coretox®. Neuronox® is marketed under different brand names, such as Botulift®, Siax®, Cunox®, and Meditoxin®.

MANUFACTURING PROCESS OF NEURONOX®, INNOTOX®, AND CORETOX®

Botulinum toxin is a biologic agent obtained from *Clostridium botulinum*, and the neurotoxin serotype and protein composition of the complex are dependent on the strain of the organism. Thus, the bacterial strain itself is one of the most significant factors in determining the characteristics of the toxin in the manufacturing process of botulinum toxin products. Neuronox®, Innotox®, and Coretox® are manufactured with BoNT-A obtained from the bacterial strain *C. botulinum* Hall A-hyper, which was originally cultivated by the University of Wisconsin. This strain is also renowned for being the source of Botox® (AbbVie, USA). During the manufacturing process of Neuronox®, it is common to use animal-derived materials to cultivate *C. botulinum*; however, in the manufacturing process of Innotox® and Coretox®, all animal-sourced materials are replaced with a non-animal-derived substitute. Following fermentation, the proteins are isolated and purified. Through varying isolation and purification processes, Neuronox® and Innotox® retain neurotoxin complex while Coretox retains only 150 kDa neurotoxin without accessary proteins. Different excipients are then added to the drug substance of each product for the purposes of stability. At the final stage, these formulated preparations are then subjected to the finishing processes. Neuronox® and Coretox® are freeze-dried, resulting in white powder for reconstitution while Innotox® is finished without any drying process, resulting in a liquid formulation. The finished medicinal product is tested prior to its release. If the medicinal product meets the potency and associated approval specifications, the product is then released for distribution and clinical use.

COMPOSITION AND FORMULATION OF NEURONOX®, INNOTOX®, AND CORETOX®

Neuronox® is a sterile lyophilized powder product for reconstitution that contains botulinum type A neurotoxin complex, human serum albumin, and sodium chloride. This formulation is another similarity between Neuronox® and Botox®, in addition to the bacterial strain and the molecular weight of the toxin. Innotox® contains the same botulinum type A neurotoxin complex, but it does not contain human serum albumin. Instead it uses L-methionine and polysorbate 20 as excipients. More strikingly, it is the first liquid BoNT-A product, with a concentration of 4 U/0.1 mL. This ready-to-use liquid formulation not only offers convenience for users, but also enhances its safety, as it eliminates the risk of contamination or inaccurate dosing caused by human error during reconstitution. Coretox®, on the other hand, contains only 150 kDa neurotoxin with no neurotoxin accessory proteins, the latter being completely removed during the purification process. Coretox® is formulated with Sucrose and then dried by lyophilization. Innotox® and Coretox® do not contain human serum albumin and they also exclude the use of animal-derived materials in the manufacturing process to eliminate the risk associated with animal-sourced proteins (Table 9.1).