

Article

Botulinum Toxin Type A Reconstituted with Lidocaine: A Report of 1000 Consecutive Cases

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Abstract: (1) Background: There is an increasing demand for a reversal of the aging process and, nowadays, more patients are seeking minimally invasive methods instead of surgery to meet this goal. The purpose of this paper is to evaluate the predictability of the off-label aesthetic use of botulinum toxin type A (BoNTA) reconstituted with lidocaine. (2) Methods: One thousand treatments, between January 2010 and January 2020, with BoNTA reconstituted with lidocaine for the rejuvenation of the upper third of the face, were performed and retrospectively evaluated. (3) Results: A few seconds after the BoNTA injections, the effect of muscle paralysis was seen in all cases; this allowed providing an optimal symmetric result with no need for a touch-up procedure at the control after three weeks. A burning sensation during the injections was claimed by almost all patients. Major complications were not registered. No touch-up procedures were required. (4) Conclusions: The results of this study show how the reconstitution of BoNTA with lidocaine may avoid imperfect results after the injections; the immediate feedback on the extent of paralysis to be expected from the chemodenervation action of BoNTA allows the physician to have immediate control of the final result.

Keywords: botulinum toxin; facial aesthetics; minimally invasive; lidocaine



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1. Introduction

In the last 20 years, the evolution of medical devices and drugs in the field of non-surgical facial aesthetics has gained popularity. Injectables such as botulinum toxin, deoxycholate, and facial fillers can be helpful in reversing facial aging and/or attaining a more attractive appearance [1–3]. The unnecessary OR and post-surgical down time and lower price of non-surgical aesthetic procedures are features that often induce patients to look for minimally invasive procedures instead of surgery. Different approaches to aesthetic improvement have been studied to avoid the facial marks of the aging processes. These approaches include, but are not limited to, the standard regional approach, which focuses on finding standard treatment points on the periocular, midface, and perioral aging areas, as well as the preauricular area; and patient-tailored techniques, which customize the points of the facial rejuvenation treatment on each patient [4].

The knowledge of medical device use has also changed: 20 years ago, surgery was the only way to reshape the nose; today, with the right choice of filler and the right injection technique, it is possible to restore nasal aesthetics without it [5,6].

To oppose the processes of natural aging due to a concatenation of exogenous and endogenous stressors, many organic and inorganic substances and various techniques have been developed and experienced, such as the intradermal microinjections of low molecular weight hyaluronic acid fragments mixed with amino acid (HAAM), which target fibroblast activity [7]. In the last 10 years, botulinum toxin has been the most-used drug in non-surgical aesthetic facial procedures [8].

The use of BoNTA is well-established in medical practice; its application extends over many indications and medical specialties such as hemi-facial spasm, strabismus, and others [9,10]. BoNTA injections are the most common non-surgical cosmetic procedures performed in the United States of America [8].

Botulinum toxin type A (BoNTA) is a potent bacterial neurotoxin produced by anaerobic bacterium *Clostridium botulinum*, which produces muscle paralysis, atrophy, and weakness [11]. The first cosmetic indication for this drug was obtained by the FDA in 2002 for the treatment of glabellar lines; in 2013, it was also approved for periorbital lines (crow's feet); and in 2018, forehead line treatments were approved [12].

Once the toxin is injected into muscles at the presynaptic nerve terminal, the heavy chain binds synaptic vesicle glycoprotein 2, causing endocytosis of the toxin-glycoprotein complex and toxin light chain release into the neuronal cytosol [11]. Toxin light chains cleave syntaxin, either synaptosomal-associated protein 25 or vesicle-associated membrane protein (VAMP)/synaptobrevin, preventing the release of acetylcholine from the axon of peripheral motor nerves and causing subsequent temporary chemical denervation and muscle paralysis [9].

Several available BoNTA preparations exist, although only onabotulinum toxin A, abobotulinum toxin A, and incobotulinum toxin A are approved for use in medical cosmetic settings.

Several papers have suggested that one toxin is superior to the others, although existing evidence suggests that experienced users should achieve equivalent results regardless of the BoNTA-A formulation [13–15].

BoNTA, before being administered, needs to be reconstituted with saline; once injected, it is necessary to wait for the onset of the drug's effect, which usually takes 21 days for a full effect, to evaluate the result and, in case of asymmetries, to perform a touch-up [11]. In the present retrospective study, we evaluated the predictability and safety of BoNTA reconstituted with lidocaine to provide a quick overview of the final result due to the transitory effect of lidocaine, whose pharmacokinetics remains the same.

2. Materials and Methods

A total of 1000 treatments in 432 patients (328 F, 104 M), between January 2010 and January 2020 were performed with BoNTA reconstituted with lidocaine for the rejuvenation of the upper third of the face. All the treatments were performed in private practice by 2 authors (R.R. and P.B.).

The exclusion criteria were: pregnancy (or pregnancy attempts); breastfeeding; neuromuscular disorders (myasthenia gravis, Eaton-Lambert disease); peripheral neuropathy (diabetes mellitus, alcoholism); aminoglycoside antibiotics therapy (e.g., amikacin, neomycin, streptomycin, tobramycin, etc.); local anesthetics allergy. All patients were aged between 28 and 62 years old.

All the three existing toxins were used: in 182 cases, incobotulinum toxin A (Bocouture, Merz Pharmaceuticals GmbH, Frankfurt, Germany) was used; in 474 cases, onabotulinum toxin A (Vistabex; Allergan, Inc., Irvine, CA, USA); and in 344 cases, abobotulinum toxin A (Azzalure, Ipsen, Paris, France). In all the cases, BoNTA was reconstituted with 2.3 mL of lidocaine (lidocaina cloridrato, Bioindustria LIM 20 mg/mL, Novi Ligure, Italy); the product was administered percutaneously with a 1 mL Luer-Lock syringe (BD, Franklin Lakes, NJ, USA) and a 30 G, 12 mm long needle (Pentaferte S.p.A., Campli, Italy).

Standard injection points were not used; for each patient, a customized treatment was administered to treat frontalis, corrugator supercilii, and procerus muscles.

3. Results

A few seconds (around 30) after the BoNTA injections, the effect of muscle paralysis was seen in all cases due to lidocaine action; this allowed the provision of an optimal symmetric result with no need for a touch-up procedure at the control after 3 weeks (Figures 1–4).



Figure 1. Case 1. A 48-year-old man before the injections of BoNTA reconstituted with lidocaine for the treatment of forehead wrinkles.



Figure 2. Case 1. Two minutes after the injections of BoNTA reconstituted with lidocaine for the treatment of forehead wrinkles.

Each patient was controlled for 3 weeks after the procedure. Major complications were not registered and in 12 cases, a monolateral (eight cases on the left side, four on the right side) periorbital ecchymosis occurred, but resolved spontaneously between 5 and 8 days. A variable amount of BoNTA units were used: 40 to 50 U in cases of onabotulinum toxin A or incobotulinum toxin A and 80 to 125 speywood U in cases of abobotulinum toxin A.

A touch-up procedure was never required to correct asymmetries and a high degree of satisfaction was reported by all patients as soon the procedure was complete; patients were surprised to see an immediate result, although a transitory burning sensation was claimed during the injections by all patients. In three cases, monolateral upper eyelid ptosis was recorded: two times with onabotulinum and one time with abobotulinum. In these cases, the ptosis was managed with the administration of Apraclonidine Chloridrato eye drops.



Figure 3. Case 2. A 33-year-old woman before the injections of BoNTA reconstituted with lidocaine for the treatment of forehead wrinkles.



Figure 4. Case 2. Two minutes after the injections of BoNTA reconstituted with lidocaine for the treatment of forehead wrinkles.

4. Discussion

Botulinum toxin is a fascinating drug that specifically targets the release of acetylcholine. Acetylcholine is a common neural transmitter that stimulates striated as well as smooth muscles and the secretion of glands such as sweat glands. After BoNTA is ingested or injected, it diffuses into the human tissue until it selectively and irreversibly binds to the presynaptic terminal of the neuromuscular or neuroglandular junction, where it exerts its actions by cleaving specific membrane proteins responsible for acetylcholine secretion [11].

Dr. Alan Scott, in the 1980s, was the first to use botulinum toxin clinically with research on strabismus and blepharospasm after using it successfully in experiments on monkeys

in the 1970s [16]. Today, BoNTA is used to treat many medical conditions, especially last year's larger dilution (microbotox) of the toxin, which has been proposed to treat several dermatological problems such as oily skin, scarring, rosacea, etc. [17].

The first study indicating the utility of BoNTA for the treatment of hyperfunctional facial lines occurred in the early 1990s by Carruthers and Carruthers [18]; during the following years, aesthetic indications and the safety of this procedure have been widely shown [19–21]. Over the past two decades, its use worldwide has transformed the aesthetic care of the aging face. Since the U.S.'s introduction of onabotulinumtoxinA in 2003 for the treatment of glabellar lines, the injection of BoNTA has become the most common aesthetic procedure performed in the United States [8].

Off-label clinical indications include hyperfunctional facial lines on the bridge of the nose, masseter and temporalis muscles hypertrophy, "golf ball chin", gummy smiles, platysmal banding, etc. [10,22–24].

In facial cosmetics, the goal of BoNTA treatment is weakening a mimetic muscle to either reduce its wrinkling effect on the skin or alter the position of a nearby facial feature (e.g., brow contour).

BoNTA is sold in vials in a lyophilized form that must be reconstituted; the reconstitution recommendation is to add 1.25 mL of saline solution in the case of onabotulinum or incobotulinum toxin A [25] and just 0.63 or 1.25 mL is required to reconstitute abobotulinum toxin A [26]. However, in the medical literature, different dilutions have been proposed and evidence shows no difference in the use of BoNTA in aesthetic indications at different dilutions [27]. Few studies have furthermore compared the use of preserved vs. non-preserved saline for reconstitution. Evidence suggests less pain is experienced by the patient while the BoNTA effects are not compromised [27].

For many years, several studies have tried to show one toxin to be superior to others, although it is almost impossible to compare the same drug in different patients using fixed doses at fixed positions of the face [28]. For example, some studies suggested onabotulinum is superior to abobotulinum: in a pilot study, 20 U of onabotulinum provided better and more prolonged efficacy than 50 U of abobotulinum for glabellar lines, as assessed by a blinded investigator; although the effect of onabotulinum apparently increased over time in the study, it was not seen in any other study or clinical practice [13]. Certain studies suggested the converse, that abobotulinum is superior to onabotulinum. Lowe et al. reported that abobotulinum (256 U total) was significantly more effective than onabotulinum (64 U total) for upper facial lines. These differences may reflect a higher abobotulinum dose than in the studies that suggest onabotulinum to be superior to abobotulinum [29].

Certain authors have suggested that protein load may influence diffusion. Aoki et al. claimed that as abobotulinum contains protein with a lower molecular mass than onabotulinum; the former will diffuse further from the injection site [30]. However, there is little evidence of clinically relevant differences in diffusion between BoNTA formulations [31–34].

In the present retrospective evaluation, lidocaine was used instead of saline for BoNTA reconstitution.

The use of lidocaine for BoNTA reconstitution has already been described: Vadoud-Seyed and Gulec, in 2007 and 2012, respectively, stated that dilution of BoNTA with lidocaine for the treatment of axillary hyperhidrosis is associated with significantly reduced pain, with the same effectiveness as saline reconstitution [35,36].

In our large case series, all patients claimed a burning sensation during the injection and patients previously injected with BoNTA reconstituted with saline claimed more discomfort when lidocaine was used; however, all patients reported a high degree of satisfaction with a quick preview of the result following the injections.

Another interesting paper about lidocaine use for BoNTA reconstitution was published in the 2000 by Gassner and Sherris. In their double-blinded, randomized controlled study, they added lidocaine to BoNTA to achieve an immediate paralyzing effect on the injected muscle (frontalis, corrugator supercilii, and procerus) [37]. In this study, lidocaine

plus BoNTA was injected only on one side of the forehead of 10 volunteer patients; the contralateral side was injected with the same dosage of toxin reconstituted in an equal volume of saline to serve as a control. With this study, the authors were able to confirm that the injection of BoNTA reconstituted with lidocaine provided the physician immediate feedback on the extent of paralysis to be expected from the chemodenervation action of BoNTA [37].

5. Conclusions

The results of our study agree with those of Gassner and Sherris and show how the reconstitution of BoNTA with lidocaine may avoid imperfect results after the injections; the immediate feedback on the extent of paralysis to be expected from the chemodenervation action of BoNTA allows the physician immediate control of the final result. When reconstituting botulinum toxin type A in lidocaine, all components retain their function. During the literature search, we did not find any specific details on why sterile saline is recommended over something else. Our assumption is that it is simply the easiest, most affordable, and predictable method to reconstitute a lyophilized drug. Supporting our assumption, several studies tried to use different reconstitution solutions and dilution.

In the present study, we used a larger amount of solution to reconstitute BoNTA; this was performed in order to have a sufficient quantity of lidocaine injected to observe muscle paralysis. However, a higher dilution can be associated with a higher toxin diffusion that theoretically can induce diffusion of the drug with unwanted effects. In the present study, we noted that a higher dilution with all the used toxins is not related to a higher record of complications such as brow or eyelid ptosis. In the present study, we recorded only three cases of monolateral superior eyelid ptosis among 1000 treatments performed (complication rate 0.03%).

The use of lidocaine instead of saline is an inexpensive procedure (the cost of one vial of 10 mL of lidocaine in Italy is about EUR 5), which allows the physician to avoid unsatisfactory results such as brow asymmetries, although it is important to explain to patients that as soon as the injection is performed, a burning sensation at the injection site is perceived for a few seconds.

To the best of our knowledge, this paper presents the largest number of treatments performed with BoNTA reconstituted with lidocaine, showing a high predictability of the procedure and a low complication rate.

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