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ORIGINAL ARTICLE

An Italian experience of a new personalized injective protocol (Botutouch) for botulinum toxin application in aesthetic medicine

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Abstract

Botulinum toxin typeA (BoNTA) is widely used in aesthetic medicine as primary treatment to reduce facial wrinkles. Major unmet needs in the field of the injection techniques include dilution factor, injected volume and site. Since 2013, an innovative protocol has been developed in our clinic that works on a double dilution volume, identifies the injection site according to the specific anatomical-functional characteristics of each patient's musculature and applies a gentle massage to the injected area to optimize the toxin spread in the muscle. We retrospectively retrieved medical records of subjects that underwent aesthetic treatments in our outpatient Italian clinics from 2013. In cobotulinum toxin A was used in double dilution (100 AU in 5 mL of physiologic solution) and followed by a gentle massage after the injection to increase the distribution into the muscle. 197 subjects, most of them drug-naïve (81.7%), underwent 869 BoNTA treatments. On average, higher total units and volumes were applied in first visits or older subjects whereas the lower ones were preferred in following visits or younger subjects. As perceived by the patients, the effects of BoNTA lasted more than 6 months in about 38% of the cases. 95.9% of subjects declared to be satisfied,whereas 5.2% of adverse events were observed (4.8% hematoma, 0.2% ptosis, and 0.2% tenderness). To date, we offer a BoNTA treatment with the aim to maximize the results and consequent patient's satisfaction, with low incidence of complications.

KEYWORDS

botulinum toxin, botutouch, facial rejuvenation, facial wrinkles, frontal lines

1 | INTRODUCTION

Botulinum toxin type A (BoNTA) is widely used in aesthetic medicine to reduce wrinkles of forehead, glabellar lines and crow's feet.[1,2] The American Society for Aesthetic Plastic Surgery included BoNTA injections in the top five nonsurgical approaches of 2018 with an overall number of 1 801 033 procedures, 16.3% more than the year before.[3] These data undoubtedly confirm the increasing use of BoNTA, although are underestimated because considering only the aesthetic use of BoNTA: this drug is not used only to reduce contractility and restore muscle tone but also to reduce the secretion of the sebaceous glands, for the treatment of bruxism, facial muscle hypertrophy, scar treatments, etc.[4]

Effective treatment and consequent patient's satisfaction also have strong emotional implications since facial mimicry supports us in social behavior and nonverbal communication.[5] Also, some authors have highlighted the positive effects of aesthetic intervention in improving depression and mood and in preventing their relapses.[6-8]

However, the standard protocol has flaws and limitations as the result is not always natural and stable. The most treated areas are glabella, forehead, crow's feet and bunny lines. The variables to be considered to set the treatment include anatomical area, gender, muscle mass, ethnicity, skin thickness, and the effects of age.[9] In addition, asymmetrical treatment can be required on the face of the same patient.[10]

The injection technique including dilution factor, injected volume and injection site can affect the efficacy of the protocol.[11] To date, various BoNTA dilutions have been proposed in literature, and this is the reason why in the clinical practice the applied dilution is at the discretion of the clinician. However, some studies have shown that a higher dilution remains effective and safe.[12,13] Since 2013, an innovative protocol has been developed in our clinic that works on a double dilution volume, identifies the injection site according to the specific anatomical-functional characteristics of each patient's musculature and applies a gentle massage to the area injected to optimize the spread of the toxin in the muscle. In this article, we want to describe our personal experience.

2 | METHODS

2.1 | Study design and population

Medical records of subjects that underwent aesthetic treatments in our outpatient Italian clinics (Palermo, Milano, Catania) from 2013, were retrospectively retrieved. Patients were included if they experienced at least one session of BoNTA injections according to Botutouch protocol as previously described by Melfa and Rauso.[14] Briefly, Incobotulinum toxin A was used in double dilution (100 AU in 5 mL of physiologic solution), thus obtaining 2 U of BoNTA each 0.1 mL of solution, and followed by a gentle massage after the injection to increase the distribution into the muscle. The injection sites were identified by asking the patient to voluntary contract the muscles relative to the treated area. In each side of the face, we usually identify six sites on the forehead (horizontal lines and eyebrows), five around the eyes (crow's feet), and one on the bunny line; glabellar lines include five sites, four between the eyebrows and one extending up the central forehead.

Baseline demographic features were collected on age and gender. The data on area, number of sites per area, units and volume of toxin of each patient's session were gathered and the dates of each session were recorded. Every subject was classified according to prior experience with BoNTA or, in other words, as naïf if the BoNTA treatment was its first treatment with any form of BoNTA.

The primary endpoint was the patient-perceived effectiveness and safety of Botutouch technique. Indeed, the assessment of the usefulness of BoNTA in aesthetic medicine is still matter of debate.[11] As this study represents a real-life experience and the patient's satisfaction is a primary goal in the context of the aesthetic medicine, we measured the primary endpoint in terms of: (a) how the patient perceives the duration of treatment. The duration of treatment was calculated as distance between two consecutive visits that were scheduled based on the patient's judgment and in agreement with the clinician; (b) patient's satisfaction relative to each session. In our clinic, we usually schedule a second visit (approximately 3 weeks from the first BoNTA injection), during which we visually inspect the effect of the BoNTA treatment and ask patients about their satisfaction.

The evaluation of tolerability included monitoring of any elicited or observed adverse events (AEs) in injection site such as edema, ptosis, bleeding, hematoma, or more generic outcomes such as pain, infection, tenderness, swelling, asymmetry, and cutaneous or subcutaneous abnormality such as erythema. All procedures performed in the study were in accordance with the Declaration of Helsinki and its later amendments or comparable ethical standards.

The informed consent form to grant the use of information and photo documents for scientific purposes was signed by the patients after being explained about the protocol of the treatment.

2.2 | Statistical analysis

The cohort features were summarized using descriptive statistics, mean and SD, median and min/max values or frequency tables, as appropriate. The difference of patient's age between the injections techniques was assessed by using Student's *t* test. Cochrane-Armitage test was applied to evaluate the trend in the use of a certain injection technique over time.

The change in distance between two consecutive visits was assessed by performing a linear mixed model for repeated measures.

3 | RESULTS

3.1 | Characteristics of the study population and injection techniques

We collected the clinical data of 197 subjects, most of them females (n = 185), with a mean age of 50.3 ± 10.3 years. One hundred sixty-one of the patients (81.7%) were naïve for BoNTA injections.

Overall, we could grouped the applied procedures into five injection patterns (called P.A50, P.B45, P.C40, P.D36, and P.E30), based on the anatomical area(s), the injection sites per area that have been treated, and the volume and units of toxin that have been injected per site.

The injection patterns (P) were named through a case letter from A to E, and a number that identifies the overall toxin units injected per visit (the number immediately after the case letter). Each technique is detailed, as below. In the P.A50 protocol, the patient needs to be wholly treated for wrinkles across the forehead except the eyebrows (20 U, four sites), the glabellar lines (10 U, five sites), the eyes (18 U, five sites per side), and the bunny line (2 U, one site per side). Compared to P.A50, in the P.B45 pattern, the glabellar lines are injected with three total units less (7 U, five sites) and the bunny line is not treated at all. Focusing into the differences, in the P.C40, the

treatment of the forehead includes the eyebrows (16 U, six sites) while the glabellar lines are not treated at all. In P.D36 a reduced dosage of the toxin is injected in the horizontal lines of the forehead (14 U, four sites), the glabellar and the bunny lines are processed as well (8 U in five sites and 2 U in 1 site per side, respectively), while eyes are partially treated (12 U, three sites per side). Finally, P.E30 pattern includes all the areas but the dosage is reduced on the whole: 10 units for the forehead wrinkles (six sites), 6 units for the glabellar lines (five sites), 12 units for the crew's feet (five sites per side), and 2 units for the bunny line (one site per side).

Table 1 summarizes the above cited characteristics of each injection pattern. In brief, the total units of BoNTA varied from 30 to 50 and the total volume from 1.45 to 2.5 mL for a comparable number of injected sites in P.A50 and P.E30, respectively. Overall, the dataset included the information about 869 visits as each subject underwent a different number of sessions (from one to 13) based on when the first treatment started.

Considering the first visit, the main performed techniques were P.A50 (74.6%; n = 142) and P.E30(25.4%; n = 50). On average, the P.A50 was performed in patients 5.3 ± 1.7 years (mean ± SE) older than those treated with P.E30 and the difference was significant (mean age of subjects at first visit: 51.8 ± 10.5 vs 46.5 ± 8.9, respectively; *P* value = .002).

Considering the first four visits, meaning more than 50% of the total sessions (n = 561; 327 for P.A50 and 234 for P.E30), we observed a significant trend ($P < .0001$) in using lower units of toxin in the later visits (Figure 1) compared to the first ones.

In subjects that experienced more than one BoNTA injection, the median distance between two consecutive sessions was 5.6 months (Figure 2) and the period was stable over time with no significant ($P = .786$) advances or delays in scheduling patient's visits as shown in Figure 3.

3.2 | Tolerability and patient's satisfaction

There were no serious AEs. Overall, we observed 5.2% (46/869) of adverse events including hematoma (4.8%, n = 42/869), ptosis (0.2%, n = 2/869) and tenderness (0.2%, n = 2/869). However, almost all subjects (95.9%) were fully satisfied and only three (one ptosis and two tenderness) out of the 46 injuries produced disappointment.

4 | DISCUSSION

This real-life study was designed to evaluate the patient-perceived effectiveness and safety of Botutouch protocol that is routinely performed in our clinics of Palermo, Catania and Milan from 2013. The results of our work emphasize that designing tailored procedures is the winning strategy in nonsurgical approach of aesthetic medicine. As customized approach is always mandatory because, as recently showed by Abramo et al,[15] different pattern of lines of the upper third of the face are related to different anatomical shape of the muscles:

TABLE 1 Characteristics (number of injected sites, total units, and volume) of the five injection techniques performed in our outpatient clinics per each anatomical area

	P.A50			P.B45			P.C40			P.D36			P.E30		
Anatomical area	Total sites	Total units	Total volume	Total sites	Total units	Total volume	Total sites	Total units	Total volume	Total sites	Total units	Total volume	Total sites	Total units	Total volume
Forehead	4	20	1.0	4	20	1.0	6	20	1.0	4	14	0.7	6	10	0.6
Glabella	5	10	0.5	5	7	0.35	0	0	0	5	8	0.45	5	6	2.5
Periocular area	10	18	0.9	10	18	0.9	10	18	0.9	6	12	0.6	10	12	0.5
Bunny lines	2	2	0.1	0	0	0	2	2	0.1	2	2	0.1	2	2	0.1
Total	21	50	2.5	19	45	2.25	18	40	2	17	36	1.85	23	30	1.45

Note: The choice of the protocol was based on individual pattern of wrinkles, patient's age, and duration of treatment.

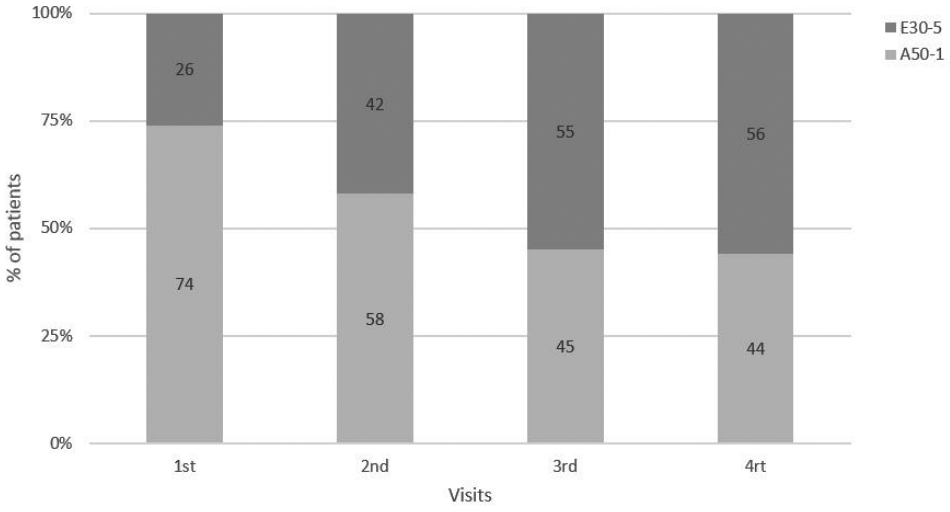

FIGURE 1 Distribution of the two main injection techniques in consecutive sessions

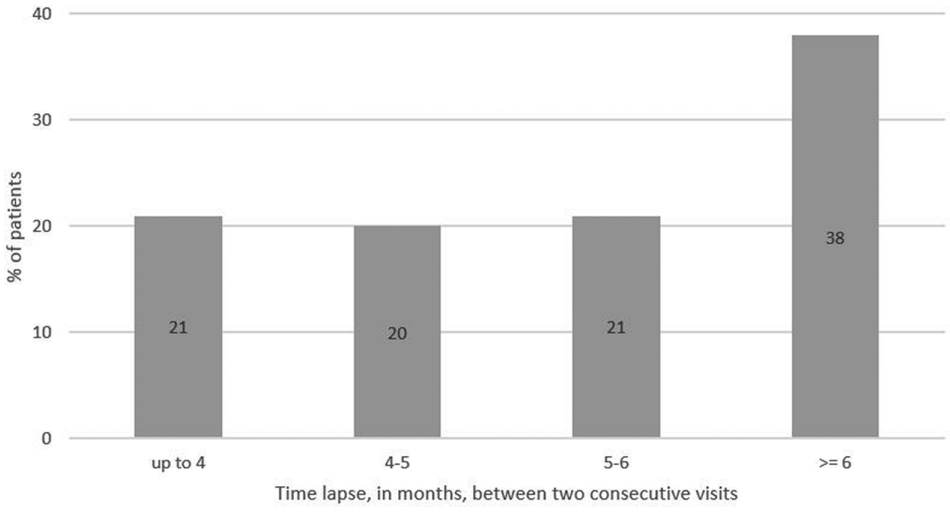

FIGURE 2 Duration of response of Incobotulinum toxin A as expressed by percentage of patients with sustained response at each time point

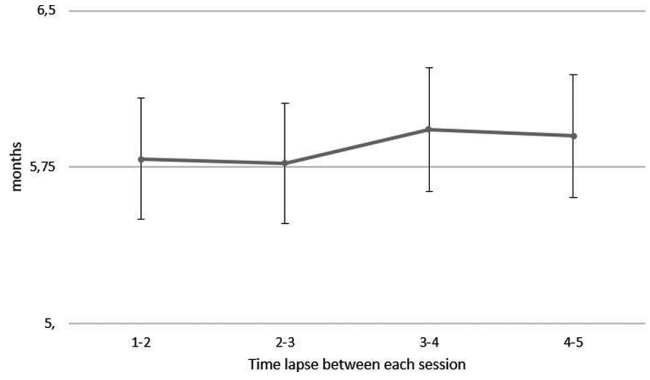

FIGURE 3 Estimated distance, in months, between two consecutive visits. The dots in the graph are mean values and the bars represent standard errors

the frontalis exhibited four anatomical shapes with four different patterns of horizontal parallel lines on the forehead skin; the corrugator supercilii showed three shapes of muscles creating six patterns of vertical glabellar lines, three symmetrical and three asymmetrical; the orbicularis oculi and procerus had single patterns.

With respect to the worldwide recommendation,[16] our procedure is different in terms of drug dilution and modality of injection, stressing the concept that the dilution of the toxin, the volume of the solution injected and the positioning of the injections have a strong influence on onset and duration of the toxin activity.[11,17] In our clinical practice, the BoNTA injections are preceded from a rigorous anatomical-functional evaluation of the wrinkles that are closely related to the individual-specific contraction of the target muscles and the effects of the age and gender. Also, we used a double dilution of BoNTA with the aim to have the toxin less concentrated and easier to be spread into the treated area.

Gassner and Sherris in 2000, in order to determine whether the paralyzing effect of botulinum toxin type A reconstituted in a solution of lidocaine with epinephrine was as effective as that of the same toxin reconstituted in saline, reconstituted in 5 mL of 1% lidocaine with 1:1 00 000 epinephrine (xylocaine 1% with epinephrine 1:1 00 000); the outcomes of the study showed that reconstituting botulinum toxin type A in lidocaine with epinephrine, all components retain their function, and no adverse effects were in the study.[18]

Moreover, also in the recent randomized comparative study of Punga et al,[13] a 2-fold injection volume was shown to be effective and safe as well as the labeled injection volume.

The analysis of our clinical records showed that the amount of the injected units was directly correlated with the age of the patient but inversely correlated with the number of previous undergone sessions. Indeed, more time the patient spent to do treatments few drug is needed to obtain the same effect over time. Thanks to this customized approach that was continuously revised at each session, the distance between two consecutive visits was maintained constant and the overall appearance improved giving a more youthful, relaxed and pleasant effect as well as perceived by the patient. As previously reported,[14] we believe that a gentle massage helps the spreading of the hyper diluted BoNTA in the injected muscle resulting in a more natural effect. In this regard, only minor adverse events were observed, and their frequency was in line with the recent literature.[19] Unfortunately, we were not able to assess the differences of the effect of Botutouch approach between genders because of the few number of males included in our cohort.

Taken together, the peculiarities of our approach result in case-by-case drug dosing adjustment and longer BoNTA activity. In conclusion, we offer a medical-aesthetic treatment with the unique need to maximize the results and consequent patient's satisfaction with low incidence of complications.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Fabrizio Melfa, Daniela Siragusa, Daniela Gaetana Caruso, Lucio Tunesi, Nicola Zerbinati, and Raffaele Rauso designed and directed the study. Fabrizio Melfa, Daniela Siragusa, Daniela Gaetana Caruso, Lucio Tunesi, Nicola Zerbinati, Fabrizio Chirico, Carmelo Lo Faro, and Raffaele Rauso wrote the manuscript. Fabrizio Melfa, Daniela Siragusa, Daniela Gaetana Caruso, Lucio Tunesi, Nicola Zerbinati, and Raffaele Rauso performed statistical analysis. Fabrizio Chirico, Carmelo Lo Faro, and Raffaele Rauso revised the manuscript. All authors read and approved the final version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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