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Multipoint and multilevel injection technique of botulinum toxin A in facial aesthetics

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Summary

Botulinum toxin represents one of the most frequently requested cosmetic procedures. We treated 223 patients with facial wrinkles using a new technique of injection of botulinum toxin A (BTA) called multipoint and multilevel injection technique (MMIT). The aim of MMIT was to relax the muscle and not paralyze it. Patient satisfaction was evaluated by Facial Line Treatment Satisfaction Questionnaire (FTSQ). Treatment with botulinum toxin determined a good response in all patients. Facial rhytids were completely resolved in case of young skin and well reduced in case of aged skin, leaving a natural aspect both in static and dynamic wrinkles. Patient mean overall satisfaction evaluated with FTSQ was 6.4 ± 1.1. In our experience, the use of botulin toxin by MMIT consents a better calibration of action with a soft and natural result. This can be achieved by distributing the BTA dose through various injection points for each area ("multipoint injections"). Furthermore, injections can be performed at different levels ("multilevel injections"). The level of injections regulates the potency of effect on the muscle: if the level is deep (intramuscular), the effect will be strong while if it is medium or superficial (subcutaneous and intradermal), the effect will be soft. This consents a fine calibration of action on muscle activity with a personal aesthetic result.

Keywords: botulinum toxin A, multipoint and multilevel injection technique, Facial Line Treatment Satisfaction Questionnaire

Introduction

Botulinum toxin is a potent neurotoxin produced by the anaerobic bacterium Clostridium botulinum. Clostridium botulinum produces seven distinct antigenic botulinum toxins, but human nervous system is susceptible only to five toxin serotypes, of which botulinum toxin A (BTA) is the most potent.[1] BTA causes muscle paralysis inhibiting acetylcholine release at the neuro-muscular junction of striated muscle.

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The discovery of the efficacy of the toxin in the improvement of glabellar rhytids was accidental.[2]

In 2002, TBA was approved by the United States Food and Drug Administration, for the treatment of glabellar rhytids. To date, many papers reported its uses on other facial sites such as the forehead, the periocular area, and other facial regions, documenting excellent results.[3–5]

Many published studies and reviews showed the safety and efficacy of BTA injection.[6,7]

Till now, the practice suggests a standard technique for the use of BTA, limiting the injection to specific intramuscular sites for each treated muscle.[5,8–11]

Our experience shows the safety and improved efficacy of a new technique of injection of BTA called

multipoint and multilevel injection technique (MMIT). MMIT consists of multiple sites and levels of injections with different dosages achieving a full zone treatment and obtaining a resolution of linear rhytids and leaving natural facial expression, always avoiding muscle paralysis.

Patient satisfaction was measured with a standard Facial Line Treatment Satisfaction Questionnaire (FTSQ) consists of a set of predetermined questions presented in a specific unvarying order, which provides strict control over interviewer behavior.[12]

Material and methods

We evaluated with FTSQ the satisfaction of 223 consecutive patients affected by facial wrinkles and treated with MMIT. All patients responding to the inclusion/exclusion criteria were recruited from the private practice of the authors from the 1st January 2010 to 1st April 2013.

Exclusion criteria were: age <18 years, inability to read and understand English, patients without at least two follow-up visit, patients suffer from a self-perception disorder (e.g., dysmorphophobia) or have unrealistic expectations, inflammation at the injection sites, neuromuscular disease (such as myasthenia gravis, Eaton-Lambert syndrome or amyotrophic lateral sclerosis), hypersensitivity to any ingredient in the formulation, including albumin, pregnancy, lactation, co-administration with aminoglycoside antibiotics or other agents that interfered with neuromuscular transmission. Pre- and post-treatment pictures were taken.

Patients removed makeup before treatment. After this, an antisepsis of the skin was carried out using nonalcoholic solution. Patients wore a disposable cap to contain hair. Before treatment, we analyzed: the facial anatomy, mimic muscular contraction, facial expression, and any pre-existing asymmetry. Important was to locate by palpation the position of muscle, its insertion point, the strength, and mass during both repose and contraction. We are looking to personalized treatment for each patient, for each side of the face and for each muscle. Pain at the injected sizes was reduced by applying topical anesthetics and cold iced devices before each injection. Micro fine 0.5 or 0.3 ml insulin syringes with a 29-G or 30-G needle were used. The drugs used were AboBotulinumToxin A Azzalure®. Azzalure® (125 Speywood U) is to be reconstituted with 0.63 mL of sodium chloride 9 mg/mL (0.9%) injection solution. This results in a clear solution containing the 125 Speywood units of the active ingredient in a concentration of 10 units per 0.05 mL of the reconstituted solution. The reconstitution is to be performed in accordance with the rules of good clinical practice, particularly with respect to asepsis.

The treatment was performed by a single doctor (I. Iozzo) in a sitting position with tangential light. One hundred and thirty-four patients were treated with MMIT to solve wrinkles of the upper face while 89 treated also the lower face and neck. The injection site was chosen in relation to the single muscle characteristics.

The dosages of the preparations are related to biological activity and are given in biological units (U). The units are termed according to the manufacturer as Speywood U (SU) for Azzalure®. The total dose is approximately 125 SU. The total dose is divided in four parts of about 30 SU each, well designed: 30 SU frontalis muscle, 30 SU for corrugator, procerus and nasal, 30 SU per orbicularis. The 30 SU remaining units may be used to solve small surface wrinkles.

The injections are carried out on skin folds due to muscles contraction and are performed at different levels (intramuscular, subcutaneous, or intradermal) in more points for each zone. In the site of strong muscular contraction, the injections were performed directly in the muscle. On the other hand, where the contraction was weak, the injection was performed at a deep or superficial intradermal level. Depth depends also on the effect we want to achieve: an intensive effect for intramuscular, a soft effect for subcutaneous or intradermal. The distribution of doses, the site injections, and their depth is reported in explicative example (Fig. 1), where the pink points indicate intramuscular injections including 3 SU, and the blue points are subcutaneous or intradermal injections consisting of 2 SU.

Corrugator muscle: three intramuscular points of injection of 3 SU each along three main lines (if the folds are only two, the doctor may run 6 SU on the greater line and 3 SU on the minor);

Procerus: two subcutaneous points of injection of 2 SU each localized on the two major skin folds;

Nasalis: two subcutaneous points of injection of 2 SU each localized on the fold of skin determined by muscle contraction;

Frontalis: five intramuscular injection of 3 SU each charged in correspondence with the two or three major skin folds determined by the muscle during its contraction.

It is possible to add one or two injection at the subcutaneous level of 2 SU each along the skin folds determined by muscle contraction at the region of smaller depth of the fold.

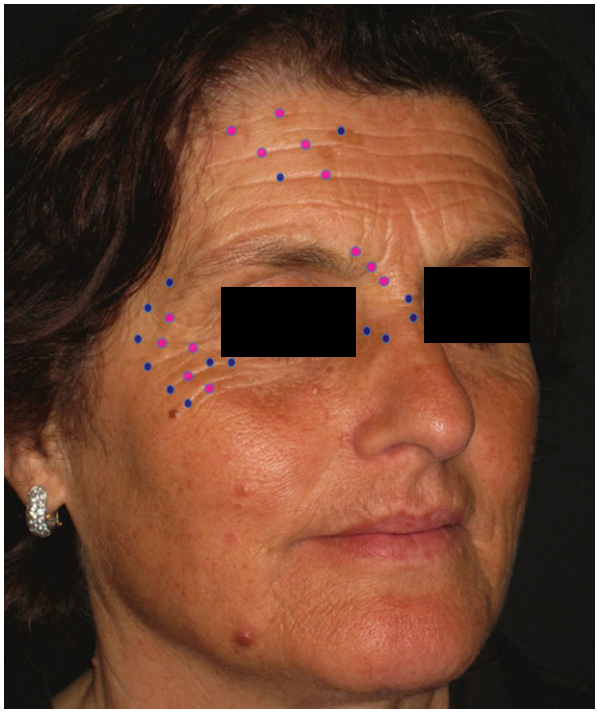

Figure 1 Distribution of points of injection. The pink points are intramuscular injections of 3 SU and the blue points are 2 SU subcutaneous or intradermal injections.

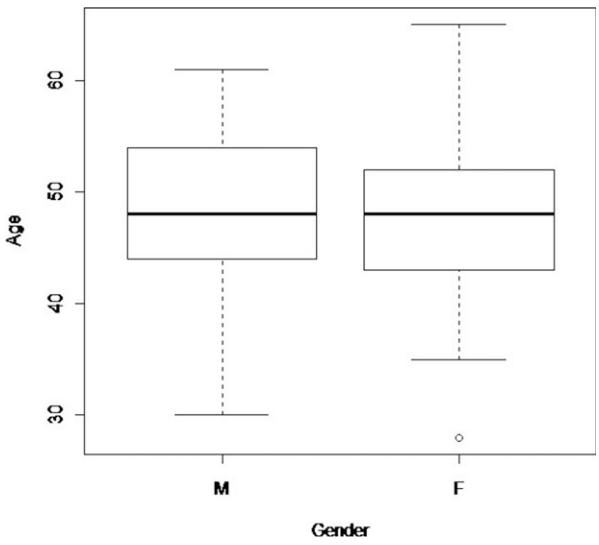

Figure 2 Boxplot age-gender.

Orbicularis: five intramuscular injection of 3 SU each, in the five major skin folds determined by the muscle during its contraction, charged on the line of the orbital frame; five injection points at the intradermal subcutaneous level practiced on certain minor folds by muscle contraction; one injection on the fold determined by the subcutaneous muscle contraction at the vertical line passing through the inner canthus of the eye; one point on the fold determined by the subcutaneous muscle contraction at the vertical line passing through the lateral canthus of the eye.

Minor changes may be tailored to the patient.

To minimize the risk of bruising, the injection of a greater number of units may remain superficial (intradermal/subcutaneous) to allow for greater action in the targeted muscle.

As the thickness of the dermis may be different, depending on skin type, age, and photo aging, it is important to evaluate each situation to avoid interferences with the injection technique.

The general post-treatment instructions for patients included staying in a vertical position and avoiding intense physical exercise or heat exposure, avoiding manipulation of the injected area for at least 6 h after treatment. In the case of ecchymosis, a cold compress or soft manual compression was applied directly to the spot where the vessels were punctured. These measures prevent the diffusion of the neurotoxin into adjacent muscles, determining a precise action.

After 2 weeks, a follow-up visit (T1) was performed and each patient was invited to complete the FTSQ. The FTSQ comprises 14 statements which respondents are asked to rate on a seven-point scale from 1 = very dissatisfied to 7 = very satisfied. If during the T1, Dr. Iozzo thought adjustments in dosing or touch-ups were necessary, they were made with additional sites and/or more units. A second follow-up visit (T2) was established to 4–6 months later.

At T2, there were a few cases of reappearance of some fine lines (that were also present before treatment in the region of the orbicularis and more rarely in the front), but thin if compared to pretreatment.

All patients gave their informed consensus for treatment, questionnaire, and iconography. Exception for glabellar lines, patients underwent BTA in other sites are informed that this treatment is off-label.

Table 1 Kaplan–Maier's estimated values of survival function

Months from the first treatment (T0)	Risk subjects	Number of retreatments	Survival function K-M
4th month	223	10	0.95
5th month	213	37	0.78
6th month	176	115	0.27
7th month	61	50	0.049

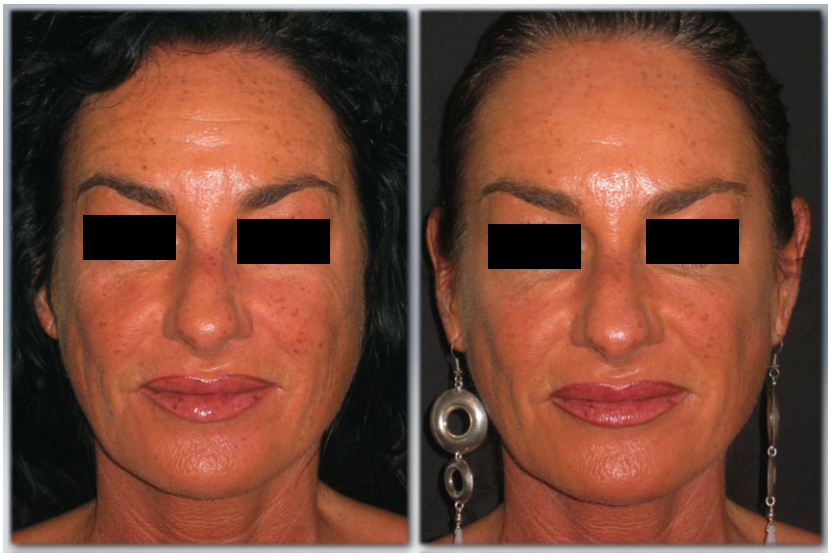

Figure 3 Frontal view: before treatment (left) and 14 days after one treatment (right).

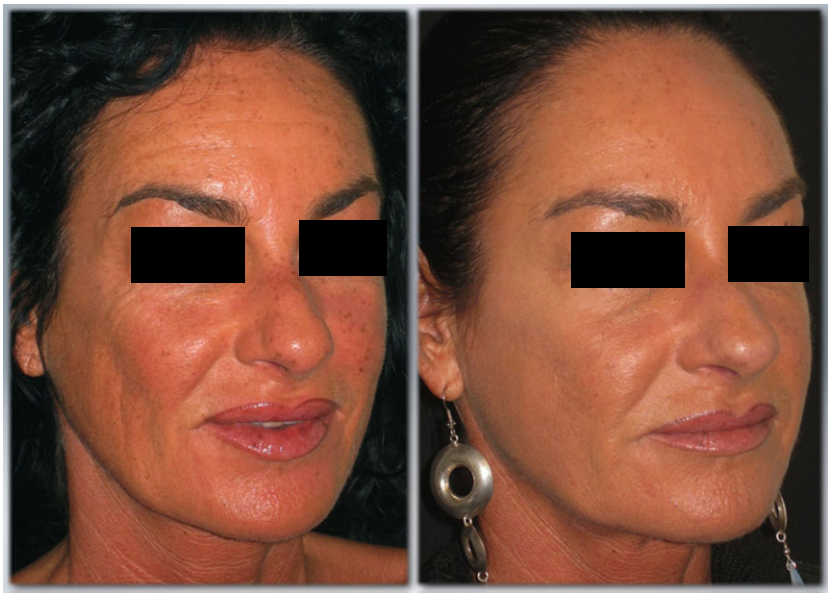

Figure 4 Oblique view: before treatment (left) and 14 days after one treatment (right).

Statistical analysis

We applied the Cox proportional hazards model. This regression model explores the relationship between the survival of patient and several explanatory variables (age, sex, duration of treatment). It consists of a risk function at baseline and a function of the covariates:

$$\lambda(t, x) = \lambda_0(t) \exp\{\beta^T X\}$$

Given that the baseline hazard function is not treated parametrically, the Cox model is a semi-parametric model. For those patients who decided to repeat the

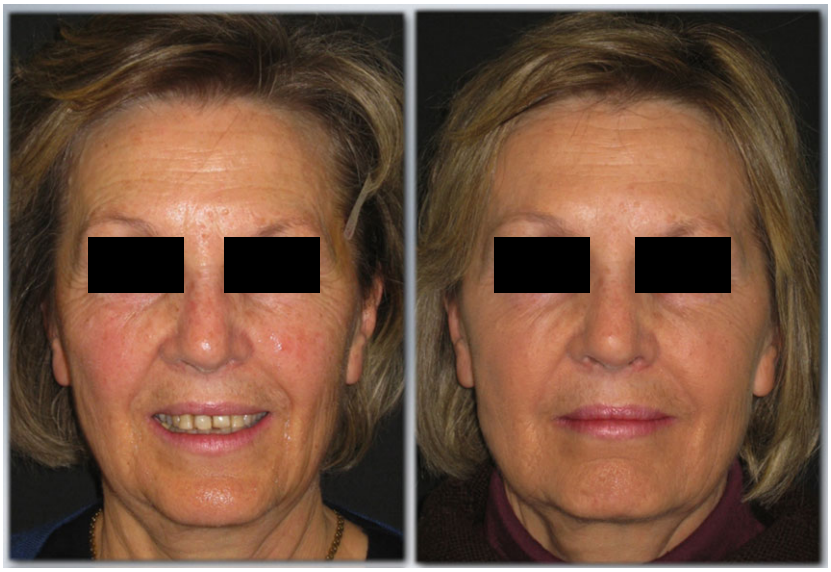

Figure 5 Frontal view: before treatment (left) and 14 days after one treatment (right).

Figure 6 Oblique view: before treatment (left) and 14 days after one treatment (right).

treatment or those patients that have been treated several times, it was mostly consequence of other factors, mostly related to the expectations of the patient about the treatment.

One statistical methodology particularly useful for this kind of analysis is the function of Kaplan–Meier. This is a nonparametric method that estimates the survival probability at time t.

The equation below is the conditional probability to survive at time t_j;

The product of the estimated P_j probabilities results in the estimation of cumulative probability to "survive" (in this study would be the probability not to repeat the treatment) at a specific time, as the subject "survived" (i.e. did not repeat) until the previous time.

All the analysis have been run through the software environment "R".

Result

The sample consisted of 223 observations, namely 198 women (89%) and 25 men (11%).

The mean ages at enrollment of patients were 48.08 ± 15.02 years for women and 42.15 ±

Table 2 Facial Line Treatment Satisfaction Questionnaire (Copyright, Allergan, Inc., 2002.)

Components of satisfaction		Satisfaction	
		Mean	SD
1	Overall satisfaction	6.4	1.1
2	Improvement in facial lines	6.1	1.2
3	Time to onset	6.1	1.1
4	Improvement in appearance	6.1	1.1
5	Look relaxed	6.1	1.1
6	Appear rested	6.4	0.9
7	Look better	6.5	0.8
8	Look younger	6.4	0.9
9	Look like you feel	6.1	1.2
10	Confidence	6	1.2
11	Competitive at work	6.2	1.1
12	Side effects	6.2	1.1
13	No sign of a procedure	6.4	1
14	No downtime	6.3	1

Satisfaction was rated in a seven-point scale using the following scale: 1 = very dissatisfied, 2 = dissatisfied, 3 = somewhat dissatisfied, 4 = neutral (neither satisfied nor dissatisfied), 5 = somewhat satisfied, 6 = satisfied, and 7 = very satisfied.

7.02 years for men, respectively. Of note, the 50% of patients is between 44 and 53 years old, and the group of men is slightly younger than the group of women.

The 60% (134) of the patients have been treated in the upper third of the face while the 40% (89) were treated also the rest of the face and neck. In this regard, there is almost the same distribution related to the age of the patients. This is clearly shown in the boxplot showed in Figure 2.

We applied Cox model to our variables, and the result is that none of the parameters is significant. This means that no linear relationship is between the variables analyzed and the risk of new performance of the treatment. Table 1 shows the estimated values of survival function di Kaplan–Maier. In all patients, we obtained a good and natural results (Figs 3–6). Regarding the FTSQ, the mean overall satisfaction was 6.4 ± 1.1. Of note, 147 (66%) patients were very satisfied. Details relating to the FTSQ are presented in Table 2. Although no severe side effects were reported, two patients reported transitory unilateral laxity of the inferior eyelid after treatment, resolved in about twenty days and probably due to exposure to high temperature (intense sun exposition) that caused toxin diffusion. Instead, two patients reported dry eyes sensation for about 3 weeks.

The smile, anger, sadness, fear, wonder, disgust, and all the other expressions of facial emotions were preserved and well manifested in all patients.

Facial wrinkles were completely resolved in the case of young skin and well reduced in the case of aged skin (Figs 7 and 8).

Of note, 20% of patients underwent a little adjustments in dosages and sites after 14 days from the starting doses.

Discussion

In the last twenty years, BTA treatment for facial wrinkles has been the most popular cosmetic procedure. Till now, the technique of application for this drug was quite standardized.[5,8–11]

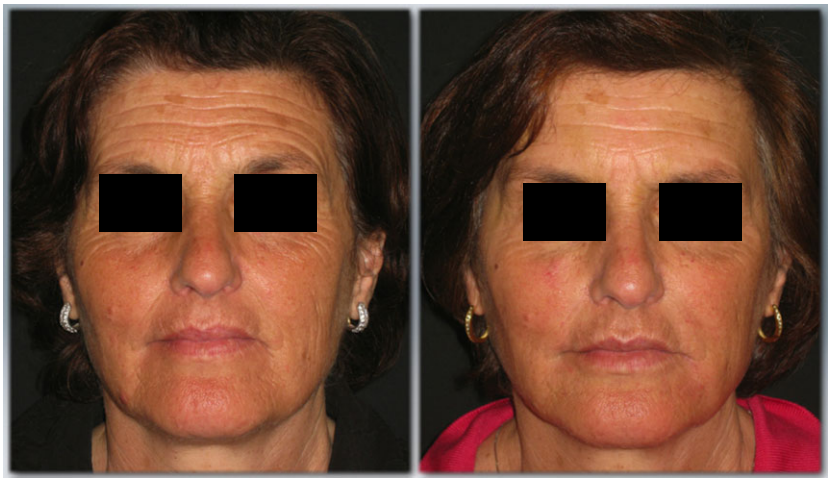

Figure 7 Frontal view: before treatment (left) and 14 days after one treatment (right).

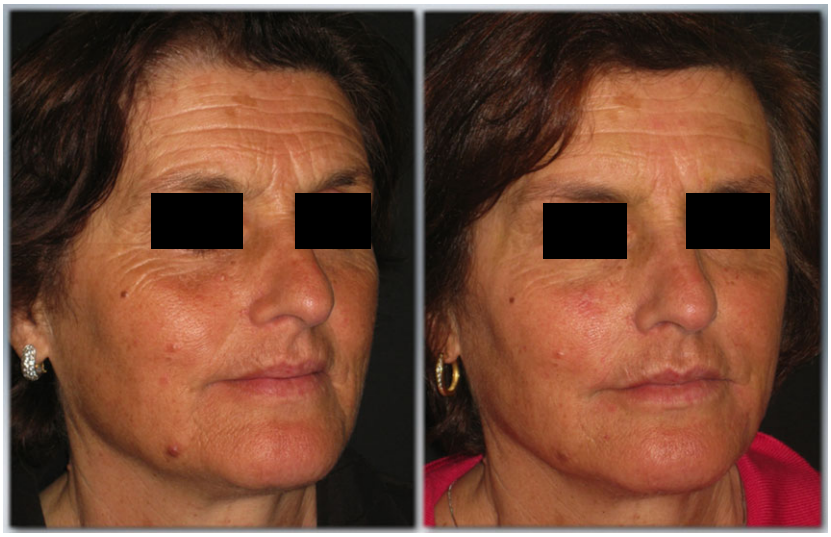

Figure 8 Oblique view: before treatment (left) and 14 days after one treatment (right).

Because of this low complication rate and relatively fast results, many treatments have been describe as "easy"; however, as with any procedure, also complications there are.[13] While formerly the aim was simply a reduction in wrinkles, now has come as aesthetic goal the harmonization of appearance and the correction of signs of aging by preserving a increasingly natural, fresh, and lively appearance.[5,14] The appearance of the face impacts self-perception, self-esteem and thus in the end effect, the quality of social contacts and interpersonal communication.[15]

In this context is that MMIT allows natural aesthetic results, avoiding local paralysis or reduction in mimic expression such as a "frozen aspect".

The aim of the new model of treatment with BTA, based on multipoint and multilevel injection technique, was to relax the entire muscle and not paralyze it, totally or in part. In the past, we spoke of transient paralysis by chemical denervation, from now we may speak of "muscular relaxation using muscle relaxant drugs".

A natural aesthetic result derives from a wide distribution of the same dose of BTA for each muscular area. In this way, we can involve in the effect of BTA not all the termination of a motor neuron and every muscular fiber, but only a part of it, so the other part of the muscle is free to move and the muscle thus appears relaxed but not paralyzed. This can be achieved by distributing the same dose through various injection points for each area ("multipoint injections"). The rule is to distribute as much as possible, treating further the areas of greatest contraction. This means that it is not necessary to completely paralyze the muscles to obtain a harmonious relaxed aspect and preserving facial expression. The final results derive from the concentration and distribution of BTA for each area.

Until now, we have spoken only of muscular injections, but injections can be performed at different levels, obtaining different effects. In fact, the injections may be directly intramuscular, subcutaneous, or intradermal ("multilevel injections"). The level of injections regulates the potency of effect on the muscle: if the level is deep (intramuscular injection), the effect will be strong while if it is medium or superficial (subcutaneous and intradermal), the effect will be soft. This consents a fine calibration of action on muscle activity, obtaining a high customization of the treatment, with a perfect personal aesthetic result.

Man is able to manifest and recognize emotion and sentiment by facial expression. Facial expression is genetic, innate, universally recognized, not dependent on race, and is fundamental for relationships between humans. For this reason, it is a very important aim to preserve this expression as much as possible.

Muscular aging together with cutaneous aging is principal component in the aging of the face. Over the years, the muscles increase their resting tone[16] and tone of contraction.

Botulinum toxin, if administered with the right rational use, can resolve this aspect of mimic muscle aging that causes hyperdynamic face wrinkles and that

makes the skin look older. The goal in treatment was a natural result (relaxation) preserving as much as possible mimicry and facial expression. The MMIT has shown to be a useful and successful technique consenting an easy application of BTA and obtaining "soft botulinum toxin" effect, with good and natural results.

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