



Effects on Emotional Perception in Aesthetic Treatment with Different Botulin Neurotoxin A Formulations

Elisa D'Agati ¹, Emanuele Ruga, ², Mohammed Saleem Alhabeel, ^{3*}, Giuseppe Ferrarelli ⁴

1, M.D. Child Neuropsychiatrist, MSc Aesthetic Medicine. Contract Professor Aesthetic Facial Medical School, Rome; Contract Professor International Medical University in Rome, UniCamillus.

2 DDS; MSc Oral surgery, Aesthetic Medicine. Specialist in Oral Surgery; SIMEO Piedmont President; Active Member of Academy of Non Transfusional Hemo-Components and Regenerative Medicine. Contract Professor University of Camerino, University of Turin; University of Oriental Piedmont. ORCID: <https://orcid.org/0000-0002-6401-9689>

3- BDS , MSc Laser Dentistry , MSc Facial aesthetics , INDBE , American Board of laser surgery , Dentist in Salamaty polyclinic Saudi Arabia

4 M.D.; DDS; MSc Aesthetic Medicine; Director and Professor Aesthetic Facial Medical School, Rome; Contract Professor International Medical University in Rome, UniCamillus.

***Correspondence to:** Mohammed Saleem Alhabeel, BDS , MSc Laser Dentistry , MSc Facial aesthetics , INDBE , American Board of laser surgery , Dentist in Salamaty polyclinic Saudi Arabia

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Received: 27 Mar 2025

Published: 03 Apr 2025

Abstract

Objective: The first aim of this study is to investigate if the aesthetic treatment of the upper face with botulinum BoNT-A could have a negative effects on emotional perception measure as “Theory of Mind”, compared the performance of patients and control subjects. The second aim is to evaluate whether there are differences in patients' ability to identify the emotions of others through facial expressions based on the type of botulinum toxin A used in the aesthetic treatment.

Method: 34 subjects were enrolled in the study. 17 patients treated with BoNT-A (9 patients (1M, 8F) were treated with onaBoNT-A, and 8 patients (1M, 7F) were treated with aboBoNT-A) and 17 control subjects (2M, 15 F mean age 46.4 years) who did not perform any aesthetic treatment during the period of the study.

All subjects underwent the “Reading the Mind in the Eyes” Test in the Italian version (task of recognition of complex mental state). The patients before and after 2/4 weeks from treatment, and controls at time T0 and after a period of 2/4 weeks at time T1. The variables of correct answer at T0 ant T1 and the always correct answers were evaluated for the statistical analysis, and the t-test was used with significance at $p < 0.5$.

Findings: Significant results emerge from the comparison between correct answers at T1 between controls (average value 26.35) vs patients (21.94) $p.01$, and always correct answers of controls (21.76) vs patients (17.53) $p.01$. Significant results emerge from the comparison between patients in the number of correct answers at T1 (onaBoNT-A average 24.22 vs. aboBoNT-A 19.38 $p.02$) and in the variable of always correct answers (onaBoNT-A average 19.44 vs. aboBoNT-A 15.38 $p.003$)

Conclusions: The results demonstrate that patients after treatment with Bont-A committed more errors than controls and there was a high variability in the answers given. This evidence demonstrates that the treatment has an effect on Theory of Mind and people's ability to identify the emotions of others through facial expressions. Our findings also showed that patients treated with aboBoNT-A make more errors at T1 than patients with onaBoNT-A in a Theory of Mind assessment task.

Keywords: Botulin Toxin, onaBoNT-A , aboBoNT-A , Theory of Mind, emotional perception.

Introduction

Injections of botulinum toxin A (BoNT-A) have become the most popular procedures in aesthetic medicine performed worldwide 1.

BoNT-A is a neurotoxin isolated and purified from the *Clostridium botulinum* type A bacteria. The pharmacological action of BoNT-A is to induce a temporary paralysis of the treated facial muscles, resulting in a reduction of facial wrinkles caused by the action of the underlying muscles. Current aesthetic uses of BoNT-A include treating glabellar lines, forehead wrinkles, periorbital and perioral lines, platysmal bands, horizontal neck lines, and the masseter, among many other applications 2.

Currently there are 3 commonly available formulations of BoNT-A: abobotulinumtoxinA (aboBoNT-A), onabotulinumtoxinA (onaBoNT-A) and incobotulinumtoxinA^{3,4}.

Despite an increased demand for botulinum toxin A injections, the clinical pharmacology and differences in formulation of commonly available products are poorly understood, moreover clinical performance, cost effectiveness and cognitive-behavioral and psychological effects of above mentioned formulations are still unclear and need to be investigated 4.

Treatment of facial muscles with BoNT-A can affect patients' psychological responses and their ability to perceive and interpret emotions in themselves and in others 5,6.

BoNT-A treatment can cause various cognitive-behavioral and psychological consequences. One consequence is related to the perception of an emotion at a personal level, while another concerns the ability to read emotions in others. Additionally, there is an impact on what a person can communicate as a result of the paralysis of certain muscles responsible for facial expressions of emotion.

Regarding the effect of BoNT-A treatment on the perception of emotion at a personal level, it can generally be stated that, when we experience an emotion like sadness, the contraction of the muscles involved in the visible expression of this emotion sends feedback to the brain areas responsible for emotional encoding, which amplifies the person's mood state. The most common explanation for the effect of BoNT-A on mood stems from the facial feedback hypothesis 7. This effect is at the basis for the use of BoNT-A on glabellar muscles in the combined treatment of depressive mood disorders 8,9,10.

Another important aspect concerning the cognitive-behavioral consequences of aesthetic BoNT-A treatment is the possibility of altering the patient's ability to interpret and read the emotions on the faces of others. When we observe others expressing an emotion on their face, we tend to replicate those movements or

respond with a facial expression that aligns with the content of what the other person is conveying through their facial expression. Mirror neurons are responsible for this characteristic, activating to improve our understanding of the emotional states of others 11. It has been demonstrated, through electromyography, that exposure to a photo where a person expresses an emotion on face activates congruent facial muscles in the observer (within less than 500 ms) 12 . Emotion recognition is the ability to read subtle cues indicating the emotional state of another person. These cues can be both visual, principally in facial expression, and verbal, both signaling an internal emotional state 13. The processing of these social cues is sometimes referred to “theory of mind” (ToM), that means the ability to attribute mental states to them self and to others ant it is necessary to predict behavior.

A study has been conducted on patients treated with BoNT-A to assess whether the temporary paralysis of certain facial muscles affects their ability to interpret the mental states of others expressed through visible emotions on faces. Patients treated with BoNT-A were shown an image of a face that changed expression over a few seconds from happy to angry. Before and after treatment, patients were asked to press a button when they perceived the peak expression of happiness, sadness, and the emotional shift. Bulnes et al. 14 demonstrated that patients after treatment recognized the emotion of anger later and were slower in recognizing the transition from a happy to an angry expression in the image shown .However, the BoNT-A works by temporarily inhibiting the transmission of nerve signals to the muscles, reducing their ability to contract 15. As a result, the treated muscles may not respond with the same speed or intensity as before, affecting facial reactivity and movement, which leads to a greater latency in response.

Different instruments have been developed to assess different components of social cognition. One of the most widely used tasks in the past two decades, particularly in the study of ToM in adults, is the “Reading the Mind in the Eyes” Test (Eyes Test) 18. Vellante et al.13 demonstrated that the Italian version of the Eyes test, in its revised, adult version, is a valid and reliable measure, which can be used to assess differences in recognition of complex affective states, including nonbasic emotions.

The first aim of this study is to investigate if the treatment of the upper face with botulinum BoNT-A could have a negative effects on emotional perception measure as theory of mind, using the “Reading the Mind in the Eyes” Test, compared the performance of patients and control subjects.

The second aim is to evaluate whether there are differences in patients' ability to identify the emotions of others through facial expressions based on the type of botulinum toxin A used in the aesthetic treatment.

Materials and Methods

34 subjects were enrolled in the study. 17 patients were treated with BoNT-A (2M, 15F mean age 49.4 years; 9 patients were treated with OnabotulinumtoxinA onaBoNT-A: 1 M, 8F, 8 patients were treated with AbobotulinumtoxinA aboBoNT-A) and 17 control subjects (2M, 15 F mean age 46.4 years) who did not perform any aesthetic treatment during the period of the study.

The treatment of patients consisted in the injection of BoNT-A in the frontal, periorbital and glabellar regions (in the complete treatment with onaBoNT-A were injected 40UM, while in the complete treatment with aboBoNT-A were injected 100US) by the same doctor specialist in aesthetic medicine.

Research tool

The “Reading the Mind in the Eyes” Test is a paper-and-pencil or online performance task where respondents are presented with 36 pictures of the eye region of a human face and asked to indicate which of the four word choices best describes what the person in the picture is thinking or feeling. Score on the test is the number of descriptors correctly identified by the participants, i.e., the number of mental states correctly identified. The maximum score is 36.

The Italian version of the “Reading the Mind in the Eyes” Test was used 13. The test is a freely available measure of facial affect recognition, easy to administer and easy to score.

Research method

All subjects underwent the “Reading the Mind in the Eyes” Test in the Italian version (task of recognition of complex mental state). The patients before and after 2/4 weeks from treatment, and controls at time T0 and after a period of 2/4 weeks at time T1.

Participants were instructed to choose which of the four descriptors best describes what the person in the photo is thinking or feeling. To avoid test retest reliability, participants could take for 10 seconds the picture and progressed to the next item when ready. Participation was voluntary and no fee or other incentive was provided for taking part in the study. All participants provided informed consent.

Statistical analysis

We analyzed the variables of correct answer at T0 and T1 and the number of always correct answer in both the sections at T0 and T1. All data were coded and analyzed using the Statistical Package for Social Sciences (SPSS) for Windows (Chicago, IL 60606, USA), version 14. All tests were two-tailed, with $\alpha = .05$. Student

t-test, was used to compare the ordinal variables.

Results

Comparison between patients and control subjects

Significant results emerge from the comparison between correct answers at T1 between controls (average value 26.35) vs patients (21.94) p.01, and always correct answers of controls (21.76) vs patients (17.53) p.01 (See Tab.1 and Fig.1).

	Patients	Control subjects	p
Gender	2 M, 15 F	2 M, 15 F	
Mean age	49.4 years	46.4 years	.13
Correct answers at T0 (mean value ± DS)	23.24 ± 3,17	24.35 ± 4,59	.20
Correct answers at T1 (mean value ± DS)	21.94 ± 5,34	26.35 ± 3,88	.01*
Always correct answers (mean value ± DS)	17.53 ± 4,73	21,76 ± 5,12	.01*

Table 1. Results of comparison between patients and control subjects

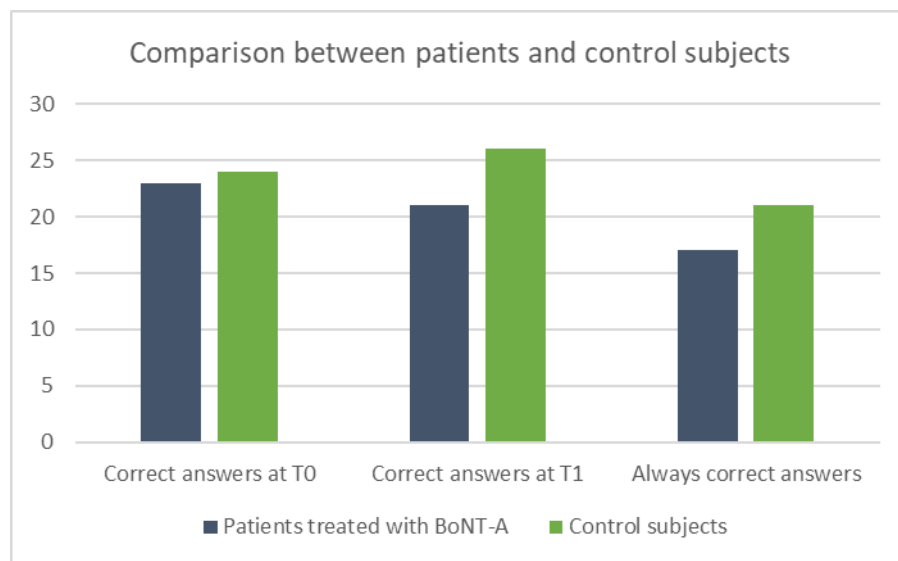


Figure 1. Schematic representation of results obtained by patients and control subjects before and after 2/4 weeks in the “Reading the Mind in the Eyes” Test

Comparison between patients treated with onaBoNT-A and patients treated with aboBoNT-A and control

subjects

Significant results emerge from the comparison between patients treated with onaBoNT-A and controls (average correct answers of patients at T1 24.22 vs controls 28.89 p.004, average of always correct answers of patients 19.44 vs controls 24.11 p.03) (See Tab. 2).

Significant results emerge from the comparison between patients treated with aboBoNT-A and controls (average correct answers of patients at T1 19.38 vs controls 28.78 p.00, average of always correct answers of patients 15.38 vs 23.33 p.00) (see Tab. 3).

	Patients treated with onaBoNT-A	Control subjects	p
Gender	1 M, 8 F	1 M, 8 F	
Mean age	50 years	45 years	.14
Correct answers at T0 (mean value ± DS)	24.22 ± 3,19	26.77 ± 5,01	.10
Correct answers at T1 (mean value ± DS)	24.22 ± 3,56	28.89 ± 3,18	.004*
Always correct answers (mean value ± DS)	19.44 ± 4,33	24.11 ± 5,81	.03*

Table 2 comparison between patients treated with onaBoNT-A and control subjects

	Patients treated with aboBoNT-A	Control subjects	p
Gender	1 M, 7 F	1 M, 7 F	
Mean age	48.75 years	46 years	.38
Correct answers at T0 (mean value ± DS)	22.12 ± 2,94	25.25 ± 4,25	.06
Correct answers at T1 (mean value ± DS)	19.38 ± 6,04	28.78 ± 7,44	.00*
Always correct answers (mean value ± DS)	15.38 ± 4,43	23.33 ± 5,46	.00*

Table 3 comparison between patients treated with aboBoNT-A and control subjects

Comparison between patients treated with onaBoNT-A and patients treated with aboBoNT-A

Significant results emerge from the comparison between patients in the number of correct answers at T1 (onaBoNT-A average 24.22 vs. aboBoNT-A 19.38 p.02) and in the variable of always correct answers (onaBoNT-A average 19.44 vs. aboBoNT-A 15.38 p.003) (see Tab. 4 and Fig.2).

	Patients treated with onaBoNT-A	Patients treated with aboBoNT-A	p
Gender	1 M, 8 F	1 M, 7 F	
Mean age	50 years	48.7 years	.38
Correct answers at T0 (mean value ± DS)	24.22 ± 3,19	22.12 ± 2,94	.09
Correct answers at T1 (mean value ± DS)	24.22 ± 3,56	19.38 ± 6,04	.02*
Always correct answers (mean value ± DS)	19.44 ± 4,33	15.38 ± 4,43	.003*

Table 4 comparison between patients treated with onaBoNT-A and aboBoNT-A

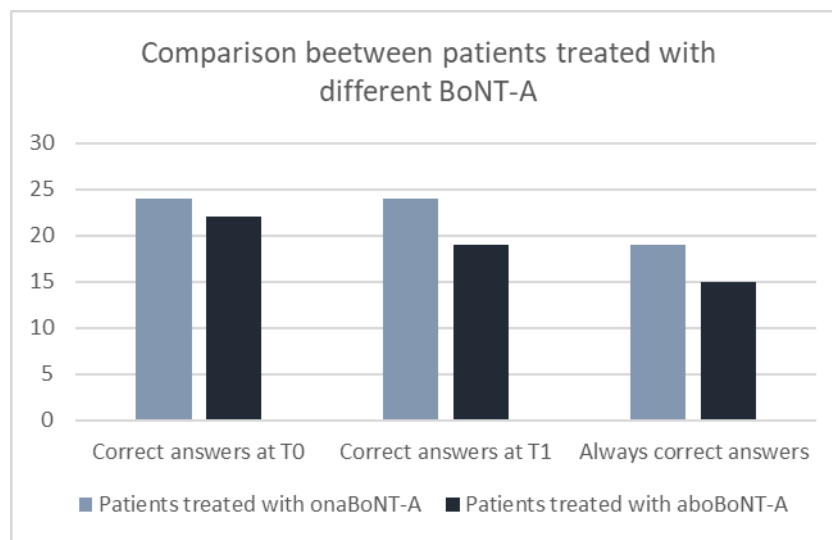


Figure 2. Schematic representation of comparison between results obtained in patients treated with onaBoNT-A and patients treated with aboBoNT-A in the “Reading the Mind in the Eyes” Test

Discussion

The results of our study show that there are significant differences in the comparison between patients and controls at time T1 in all the investigated variables (number of correct responses, and always correct responses at time T0 and T1). It was observed in the patient group that there is a tendency to make more errors after treatment, and there is high variability in the number of correct responses before and after the BoNT-A treatment.

All controls subjects, when retested, responded more correctly, making fewer errors, which is understandable due to the effect of familiarity with the test. The same cannot be said for the patients, as at time T1, they

made more errors than the controls, and there was high variability in the responses, with a decrease in the always-correct responses compared to the controls.

Our results demonstrate that treatment of the upper third of the face with BoNT-A has an effect on Theory of Mind and the ability of individuals to interpret and read the emotions of others through facial mimicry. Therefore, it is possible to hypothesize that the temporary inability to contract certain facial muscles has made the patients involved in the study less capable of mimicking and interpreting the emotions presented in the “Reading the Mind in the Eyes” test. Figure 3 show the different ability to express an emotion of surprise and anger in one of the patients treated with BoNT-A before and after treatment in this study. It is also described that botulinum toxin can cause dysfunction of face harmony and, as a result, complex psychosocial disturbances can occur and may affect social interaction and cause flattening of affect 17 .

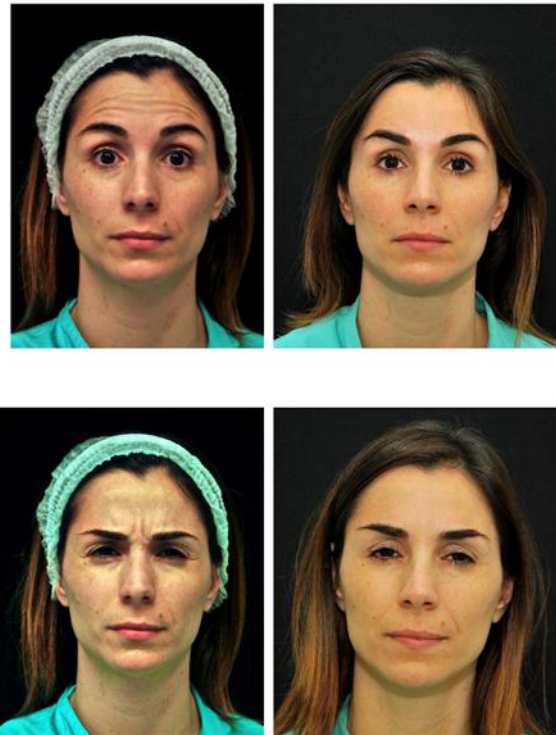


Figure 3. The images show the different ability to express an emotion of surprise and anger in one of the patients treated with BoNT-A before and after treatment.

Our results confirm the finding of a previous study in which the researchers, using the Eye Test, found significant differences in patients before and after treatment with botulinum toxin in the frontal and periorbital areas 18 , but the sample was smaller (12 subjects), and there was no comparison with a control

group or a comparison between the effects of different type of BoNT-A.

The comparison of the results obtained by patients treated with onaBoNT-A versus patients treated with aboBoNT-A showed that there are differences on the base of the BoNT-A used in the treatment.

Patients treated with aboBoNT-A obtained fewer correct answers at T1 compared with patients treated with onaBoNT-A. There is also a significant major variability in the number of always correct answers in patients treated with aboBoNT-A.

It is possible to hypothesized that aboBoNT-A may determine a more powerful action on the mimic muscles involved in the treatment, thus having a greater influence on skills related with Theory of Mind and the ability to detect emotions in others. Our finding could be related with literature study that demonstrate differences in the specific potency and efficacy of different type of BoNT-A^{3,4,19}. showed that the specific potency of the 150 kD BoNT-A neurotoxin was calculated as 137 units/ng for onaBoNT-A, 154 units/ng for aboBoNT-A, and 227 units/ng for incoBoNT-A. These results demonstrated that incoBoNT-A contains the highest specific neurotoxin activity, followed by aboBoNT-A, with onaBoNT-A having the lowest specific activity 19 .

However, all treated patients were satisfied of the aesthetic results in the treatment of the wrinkles.

The use of botulinum toxin in the treatment of expression and static wrinkles is an essential procedure for doctors specializing in aesthetic medicine. However, this treatment impacts facial mimicry, which is fundamental both on a personal and social level. Every expression on our face tells something and, above all, sends a message to those who observe us. This study demonstrate that the common BoNT-A treatment could affect the patient's ability to identify the emotions of others through facial expressions. It is crucial for the aesthetic physician to find the right balance between the efficacy of aesthetic treatment, the modulation of facial mimicry, and do not alter the information that our brain uses, though the contraction of mimic muscles, for the ability to detect emotion.

Although the "Reading the Mind in the Eyes" Test is one of the most widely used tasks in the study of ToM in adults, one limitation of our study is that the stimuli used in the test consist of photos of parts of the face, which are less rich than stimuli encountered in real-life contexts, both because they do not depict the entire face and because they do not reproduce the kinetic aspects of emotional expression. For these reasons, it is possible to hypothesize that the performance on the test likely underestimates the abilities that could be observed in the presence of more informative stimuli. However, all control subjects performed better the second time they were tested, and only the patients didn't do the same.

Conclusions

The results demonstrate that patients after treatment with BoNT-A committed more errors than controls and there was a high variability in the answers given. This evidence demonstrates that the treatment has an effect on Theory of Mind and patient's ability to identify the emotions of others through facial expressions. Our findings also showed that patients treated with aboBoNT-A make more errors at T1 than patients with onaBoNT-A in a Theory of Mind assessment task.

Future studies should include a larger sample, assess whether there are gender differences, and compared patients treated with the same BoNT-A on the base of different number of units administered, in the hope of being able to obtain the perfect balance between the aesthetic result and the ability to recognize emotions in other people.

Authors' contributions

ED Collection and interpretation of data ED,GF,ER,MSA Analysis, interpretation of data and writing of manuscript. ED performed the statistical analyses of the data. ED,ER, GF ,interpretation of the results and in the review and final approval of the manuscript.

Conflicts of interest

All authors declared that there are no conflicts of interest

Ethics approval and consent to participate

All patients provided their informed consent to participate in the study. As required by applicable local regulations, this study adhered to all local regulatory requirements .The study was conducted in accordance with the protocol, Guidelines for Good Clinical Practice, and the ethical principles laid down in the Declaration of Helsinki.

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