



Botulinum toxin-A in the treatment of upper facial wrinkles: Efficacy comparison of different formulations

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Abstract

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Aim: It is suggested that different formulations of botulinum toxin-A (BoNT-A) used for the same indication might be a factor affecting patient satisfaction. This study aimed to assess patient satisfaction levels in treating upper facial wrinkles (UFW) using various BoNT-A formulations and their association with age and gender.

Materials and Methods: This retrospective study included 600 UFW patients treated with different formulations of BoNT-A. The BoNT-A formulations included three different groups: onaBoNT-A (ONA, n:200), aboBoNT-A (ABO, n:200), and praBoNT-A (PRA, n:200). In the patient files or records, satisfaction levels from the BoNT-A application were scored as follows: 1: not satisfied, 2: slightly satisfied, 3: satisfied, 4: very satisfied, 5: completely satisfied.

Results: The mean patient satisfaction scores for the ONA and ABO groups were similar, and were higher compared to the PRA group (4.4 ± 0.5 vs. 4.3 ± 0.6 vs. 4.0 ± 0.9 , $P < 0.001$, respectively). The mean satisfaction score of the patients aged 18-30 and those aged >60 were lower than the other age group. Among all patients in the 41-50 age range, the patient satisfaction score was higher in the ONA group than the ABO and PRA group. In all female patients, the mean satisfaction score was lower in the PRA group compared to the ONA and ABO groups ($P < 0.001$).

Conclusion: While various BoNT-A formulations are generally associated with high patient satisfaction in the treatment of UFW, this can vary depending on age ranges and gender. Evaluating patient-related factors such as age and gender can contribute to the treatment planning for UFW and enhancing treatment adherence.



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Introduction

Upper facial wrinkles arise due to the repeated contraction of facial muscles and dermal atrophy [1]. In aesthetic procedures, injections of botulinum toxin (BoNT), typically given beneath the skin or directly into the muscle, are commonly used. Key muscles targeted in these treatments are the orbicularis oculi, procerus, corrugator supercilii, and frontalis [2]. Derived from the anaerobic fermentation process of the *Clostridium botulinum* bacterium, BoNT, when administered in low doses to muscles, inhibits acetylcholine activity at the neuromuscular junction. This leads to a temporary chemical denervation in muscle fiber function, resulting in localized muscle relaxation and a reduction in the appearance of wrinkles. The influence of the toxin remains for a duration of 2 weeks up to a month, with its potency waning or vanishing within a 3 to 4 month period [3].

Clostridium botulinum bacterium generates toxins in eight unique serotypes, labeled A-H, each immunologically distinct. For the treatment of upper facial wrinkles, serotype-A is usually preferred [4]. In clinical practice, BoNT-A has different commercial preparations available, including onaBoNT-A (ONA) as *Botox*(®), aboBoNT-A (ABO) as *Dysport*(®), and praBoNT-A (PRA) as *Nabota*(®) [5]. It has been reported that the application of BoNT not only treats dynamic wrinkles but can also enhance skin quality over the long term [6].

In the treatment of upper facial wrinkles, factors such as the patient's age, gender, expected duration of the treatment's effects, the patient's expectations from the treatment, and the cost of the treatment should be considered. Once these factors are thoroughly assessed, the right dosage should be administered to the suitable regions. Moreover, these factors can influence patient satisfaction, which is an essential indicator of success in aesthetic procedures [7]. It is suggested that different formulations of

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BoNT-A used for the same indication might be a factor affecting patient satisfaction [8-10]. While various studies have indicated similar durations of effect and response rates for different BoNT-A formulations [11, 12], one study has highlighted a quicker effect duration for ABO [13]. However, there are a limited number of studies on this topic, and their results are conflicting. Therefore, this study aimed to evaluate the differences in patient satisfaction levels in the treatment of upper facial wrinkles with different BoNT-A formulations as well as the relationships between these differences and age and gender.

Materials and Methods

This retrospective study involved a review of medical records of patients who received BoNT-A treatment for upper facial wrinkles at the Private Clinic between January 2022 and December 2022. Before initiating this retrospective review, approval was obtained from the Istanbul University Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (Date: 09.08.2023, Decision No: 753514). All procedures for data collection and analysis adhered to ethical rules and principles of the Declaration of Helsinki.

Study population

A total of 1,034 patients who were treated with different formulations of BoNT-A for upper facial wrinkles were evaluated retrospectively. Patients were excluded if they had known psychiatric comorbidities and dysmorphic disorders, underwent other aesthetic procedures in the upper facial region, received BoNT within the last 6 months, had injections for upper facial wrinkles within the last year, had a history of pregnancy, lactation, or neuromuscular disease, or did not fill out the patient satisfaction form. After the exclusion process, the analysis included 600 patients who were treated with different formulations of BoNT-A for upper facial wrinkles.

Study protocol

The clinic's electronic information system and patient files were used to gather demographic and clinical data. Upper facial wrinkles were considered as glabellar, periorbital, and frontal wrinkles. Patients were divided into three groups: those treated with ONA (n = 200), those treated with ABO (n = 200), and those treated with PRA (n = 200). In the patient files or records, satisfaction levels from the BoNT-A application were scored as follows: 1: not satisfied, 2: slightly satisfied, 3: satisfied, 4: very satisfied, 5: completely satisfied.

Administration of BoNT-A

ONA was diluted with 2 cc saline for 100 units, ABO with 3 cc saline for 500 units, and PRA with 2 cc saline for 100 units. Before the treatment, patients' faces were cleaned with 0.9% saline solution. Treatment was administered to all patients on the orbicularis oculi, procerus, corrugator supercilii, and frontalis muscles in the upper facial region. Dosages were determined based on individual patient needs. For the frontal muscle, dosages ranged between 15-20 units for ONA, 40-50 units for ABO, and 15-20 units

for PRA. For the glabella, dosages ranged from 15-20 units for ONA, 60-80 units for ABO, and 15-20 units for PRA. In the periorbital area, dosages of 20-25 units of ONA and PRA, and 40-60 units of ABO were administered.

The toxins were administered intramuscularly using a 33-gauge needle. For the glabellar wrinkles, the toxin was applied just above the medial end of the corrugator supercilii muscle, and for the procerus muscle, it was applied to the midpoint of the glabellar region. For frontal wrinkles, a symmetrical application was made starting 1.5 cm above the eyebrow to the areas where the muscle contracts. For periorbital wrinkles, the application was made 1.5 cm away from the lateral canthus and 1 cm below and above this point.

Statistical analysis

All data were analyzed with STATA/MP v.16 software (StataCorp LLC, Texas, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean \pm standard deviation values. Student t-test was used for comparisons between two groups. ANOVA test (post-hoc: Bonferroni test) was used for comparisons between more than two groups. Categorical variables were presented as numbers and percentages, and comparisons between groups were performed using Chi-square and Fisher exact tests. For the Chi-square analysis in R x C contingency tables, the Bonferroni adjustment was applied [14]. Significance was accepted at $p < 0.05$ (*) for all statistical analyses.

Results

The mean age of the patients included in the study was 47.9 ± 12.6 years (range: 24 - 78 years), and the vast majority were female (88.2%). The mean age did not show significant differences between the treatment groups ($p > 0.05$). The rate of male was higher in the ABO group compared to the other groups, while it was similar in the ONA and PRA groups (ONA: 9.0% vs. ABO: 17.5% vs. PRA: 9.0%, $P = 0.014$). While the mean satisfaction score was similar in the ONA and ABO group, it was higher in

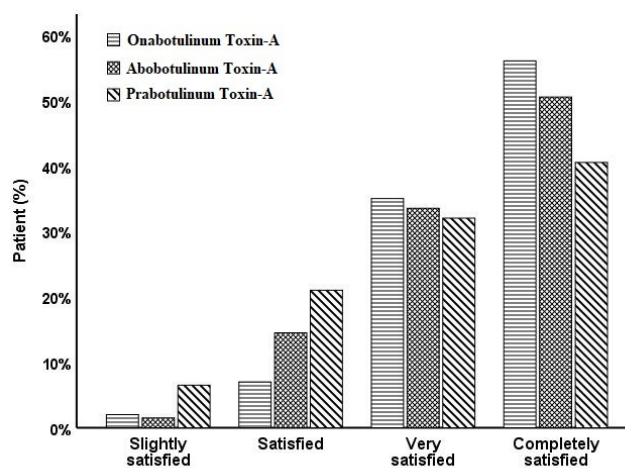


Figure 1. Satisfaction of upper face wrinkles patients treated with different formulations of botulinum toxin-A.

Table 1. Demographic characteristics and satisfaction scores of upper face wrinkles patients treated with different botulinum toxin-A formulations.

Variables	ONA	ABO	PRA	p value
	n = 200	n = 200	n = 200	
Age, years	49.1 ± 11.1	47.8 ± 10.8	46.8 ± 14.3	0.187
18-30, n (%)	9 (4.5)	10 (5.0)	41 (20.5)	
31-40, n (%)	41 (20.5)	42 (21.0)	35 (17.5)	
41-50, n (%)	69 (34.5)	69 (34.5)	46 (23.0)	<0.001*
51-60, n (%)	45 (22.5)	47 (23.5)	37 (18.5)	
>60, n (%)	36 (18.0)	32 (16.0)	41 (20.5)	
Gender, n (%)				
Female	182 (91.0)	165 (82.5)	182 (91.0)	
Male	18 (9.0)	35 (17.5)	18 (9.0)	
Patient satisfaction score	4.4 ± 0.5	4.3 ± 0.6	4.0 ± 0.9	<0.001*
Not satisfied, n (%)	0	0	0	
Slightly satisfied, n (%)	4 (2.0)	3 (1.5)	13 (6.5)	
Satisfied, n (%)	14 (7.0)	29 (14.5)	42 (21.0)	<0.001*
Very satisfied, n (%)	70 (35.0)	67 (33.5)	64 (32.0)	
Completely satisfied, n (%)	112 (56.0)	101 (50.5)	81 (40.5)	

Data are mean ± standard deviation or number (%). *p<0.05 indicates statistical significance. Bold characters indicate differences between the groups. Abbreviations: ONA, onabotulinum toxin-A; ABO, abobotulinum toxin-A; PRA, prabotulinum toxin-A.

Table 2. Relationship of satisfaction scores with age and gender in each botulinum toxin-A formulation group.

Variables	Patient satisfaction score					
	ONA	p value	ABO	p value	PRA	p value
	n = 200		n = 200		n = 200	
Age						
18-30	4.0 ± 0.9		4.0 ± 0.4		4.0 ± 0.5	
31-40	4.5 ± 0.5		4.4 ± 0.5		4.5 ± 0.4	
41-50	4.6 ± 0.3	<0.001*	4.3 ± 0.6	0.048*	4.3 ± 0.5	0.012*
51-60	4.5 ± 0.5		4.4 ± 0.5		4.4 ± 0.5	
>60	4.0 ± 0.8		4.0 ± 0.6		3.8 ± 0.8	
Gender						
Female	4.5 ± 0.7	0.559	4.4 ± 0.8	0.493	4.1 ± 0.9	0.827
Male	4.4 ± 0.6		4.3 ± 0.7		4.2 ± 1.0	

Data are mean ± standard deviation or number (%). *p<0.05 indicates statistical significance. Bold characters indicate differences between the groups. Abbreviations: ONA, onabotulinum toxin-A; ABO, abobotulinum toxin-A; PRA, prabotulinum toxin-A.

these group compared to the PRA group (ONA: 4.4 ± 0.5 vs. ABO: 4.3 ± 0.6 vs. PRA: 4.0 ± 0.9, P < 0.001) (Table 1). In each treatment group, the majority of the patients were “very satisfied” or “completely satisfied” (Figure 1).

In all patients, the mean satisfaction score of the patients aged 18-30 and those aged 60 and above were lower compared to the other age groups (p<0.05) (Table 2). On the other hand, in all patients aged 41-50, the mean satisfaction score was higher in the ONA group compared to the ABO and PRA groups (p<0.001). In other age groups, the BoNT-A formulation groups had similar mean satisfaction scores (p = 0.158 for patients aged 18-30, p = 0.108 for patients aged 31-40, p = 0.088 for patients aged 50-60, p = 0.150 for patients aged >60).

In each BoNT-A formulation group, the mean satisfac-

tion scores were similar between male and female patients (Table 2). Besides, in all female patients, the mean satisfaction score was lower in the PRA group compared to the ONA and ABO groups (p<0.001), while the ONA and ABO groups had comparable mean satisfaction scores (p = 0.995). However, in all male patients, the average satisfaction score was similar across the BoNT-A formulation groups (p = 0.269).

Discussion

This is the first study comparing patient satisfaction levels with ONA, ABO, and PRA formulations in individuals with upper facial wrinkles. The mean patient satisfaction scores for the ONA and ABO groups were similar, and were higher than the PRA group. Among all patients in the 41-50 age range, the patient satisfaction score

was higher in the ONA group than the ABO and PRA group. In all female patients, the mean satisfaction score was lower in the PRA group than the other group.

BoNT-A preparations are widely used in cosmetic dermatology practice to improve the appearance of upper facial wrinkles [15]. Upper facial wrinkles can be perceived as indicators of the aging process by patients, potentially influencing their quality of life and self-assurance. Consequently, patients might express a desire for the treatment of upper facial wrinkles. Treatment satisfaction is significant as it correlates with patients' psychosocial well-being. Patients' contentment with the treatment not only reflects the success of the intervention but also impacts their adherence to further treatment [16].

Previous studies have reported that ABO or PRA have similar efficacy to ONA [8, 17, 18]. However, the results regarding patient satisfaction with different BoNT-A formulations in the literature are contradictory. Several studies have frequently compared two BoNT-A formulations [19, 20]. Some studies have reported better patient satisfaction in patients treated with ONA [8, 9]. Conversely, it has also been shown that ONA treatment exhibited similar or lower patient satisfaction levels compared to ABO or PRA treatments [9, 10]. In the current study, the ONA and ABO groups had similar patient satisfaction scores. These groups exhibited higher patient satisfaction scores compared to the PRA group. In a study evaluating the effectiveness of ONA and PRA treatments on glabellar and frontal wrinkles, equal amounts of ONA and PRA injections were administered to opposite sides of the face. The onset of effects and patient satisfaction did not differ on both sides of the face. However, there was a partially elevated trend in patient satisfaction within the ONA treatment group [21]. Differences among studies could be related to the characteristics of the patient populations.

Patient satisfaction can be influenced by variables such as age, gender, individual expectations, and previous treatments [8]. While the utilization of BoNT-A for addressing upper face wrinkles exhibits a rising tendency among male patients, it is more considerably widespread among female patients [8, 17]. Men possess a greater muscle mass (particularly in facial structures), a less dense fat layer, and increased facial mobility compared to women, all of which can contribute to the formation of severe wrinkles. Additionally, they have a higher number of toxin receptors, which could lead to variations in the duration of effect or dosage of different BoNT-A formulations [22]. In a study conducted on male patients receiving ONA and PRA treatments, the rates of treatment response were higher in the PRA treatment group [23]. In another study comparing the effects of ONA and PRA treatments on glabellar wrinkles, 90% of the patients were female, and treatment responses were similar across treatment group [24]. In the present study, the satisfaction score was notably lower in favor of PRA among female patients. Additionally, there was a trend towards reduced scores in male patients who underwent PRA treatment. These findings suggest that gender-specific factors might lead to variations in the efficacy of different BoNT-A formulations [25].

In the APPEAL study, which included patients receiving a minimum of three ABO injections for glabellar lines, the

majority of patients were female and aged 41 or above. Following the third ABO treatment, 74.1% of patients reported being "very satisfied", and 25.2% reported being "satisfied" [26]. While this condition was higher in female patients than male patients, it was lower among patients aged 60 and above [26]. In the current study, satisfaction scores were higher among patients aged 41-50 receiving ONA treatment. Besides, patients aged 18-30 and those aged 60 and above who underwent BoNT-A treatment displayed lower satisfaction scores compared to other age groups. While patients aged 18 to 30 and those aged 60 and above are reported to have a more negative perception of their age (appearing younger) or 'negative feelings,' patients aged 41 to 50 exhibited the highest rates of positive responses towards both factors [27]. On the other hand, considering the reduced skin thickness and elasticity, weaker facial muscle tone, and the predominance of wrinkles attributed to gravitational forces rather than muscular contractions over time in older individuals, it is not expected that the elderly would exhibit a superior response to BoNT-A in comparison to other age groups [28]. Furthermore, different serotypes of BoNT-A may exert their efficacy through distinct molecular mechanisms [25]. In general, these findings support the notion that the efficacies of different formulations in BoNT-A treatment may be influenced by factors such as age and gender among patients [8].

While this study boasts a larger population compared to the existing literature, it does have some important limitations. This study had a retrospective design. Therefore, it did not evaluate other variables such as patients' pre-treatment expectations that could influence patient satisfaction with BoNT-A treatment, previous treatments, and variations in the duration of treatment effects [29-31]. The relationship between the duration of action of BoNT-A formulations and the formation of neutralizing antibodies is not yet fully understood. During this process, patient-related factors such as age and gender may play a significant role [31]. On the other hand, it has been reported that ONA's biological activity is higher than that of incoBoNT-A, which is not present in the current study, and it provides better patient satisfaction [32, 33]. Besides, it has been reported that DaxiBoNT-A, a new formulation of BoNT-A, provides a higher response rate and a significantly longer duration of effect compared to ONA [34, 35]. Prospective studies including different BoNT-A formulations matched for gender and age ranges can provide valuable insights into both this process and the variations in patient satisfaction associated with formulations.

Conclusion

Different BoNT-A formulations in the treatment of upper facial wrinkles were mostly associated with high patient satisfaction. While patients of younger or older age exhibited lower levels of patient satisfaction, those within the middle age group demonstrated higher patient satisfaction scores in favor of ONA treatment. Therefore, evaluating patient-related factors such as age and gender can contribute to the treatment planning for upper facial wrinkles and enhancing treatment adherence.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Financial disclosure

The authors declared that this study has received no financial support.

Ethical approval

Before initiating this retrospective review, approval was obtained from the Istanbul University Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (Date: 09.08.2023, Decision No: 753514). All procedures for data collection and analysis adhered to ethical rules and principles of the Declaration of Helsinki.

Author contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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