

OnabotulinumtoxinA Dose-Ranging Study for Hyperdynamic Perioral Lines

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BACKGROUND Few dosing data on onabotulinumtoxinA to treat hyperdynamic perioral lines (POLs) are available. Studying onabotulinumtoxinA in controlled settings is beneficial to treating a hyperfunctional orbicularis oris.

OBJECTIVE To compare the dose-response relationship of two doses of onabotulinumtoxinA in hyperdynamic POLs.

METHODS Female subjects ($N = 60$) received injections of onabotulinumtoxinA at four sites totaling 7.5 U or 12.0 U. Subjects returned at weeks 2, 4, 8, 12, 16, and 20. POL severity and total lip satisfaction (TLS) were assessed at all visits.

RESULTS Investigator-assessed POL severity was reduced through week 20 for 12.0 U ($p < .01$). POL reduction for 7.5 U persisted until week 16 ($p < .05$). Responder rates did not differ until week 12 (12.0 U, 77%; 7.5 U, 36%; $p = .003$). Subject-assessed TLS was improved ($p < .05$) at all time points for both groups except at week 20 (12.0 U; $p = .06$). Most adverse events (AEs) were mild to moderate in severity and typical for onabotulinumtoxinA treatment in the lips, and the incidence was dose-dependent.

CONCLUSION OnabotulinumtoxinA provides significant reductions in POL severity and high levels of subject satisfaction. Lack of dose response and fewer AEs suggest that treatment of hyperdynamic POLs with 7.5 U appears adequate for up to 16 weeks.

Drs. Cohen, Cox, and Dayan have served as consultants and investigators for Allergan, Inc.

The use of onabotulinumtoxinA (BOTOX Cosmetic, Allergan, Inc., Irvine, CA) in facial aesthetics represents an effective and well-researched therapy for the treatment of hyperdynamic facial rhytides.¹⁻⁴ OnabotulinumtoxinA is the most widely studied neurotoxin, with more than 2,100 peer-reviewed publications covering cosmetic and thera-

peutic use.⁴ Its minimal invasiveness, lack of downtime, and low risk of serious complications make it an attractive treatment option for patients and physicians.⁵ For these reasons, treatment with onabotulinumtoxinA has been the most popular noninvasive cosmetic procedure since the U.S. Food and Drug Administration approved it for cosmetic use.⁵⁻¹⁰

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The safety and efficacy of onabotulinumtoxinA in glabellar frown lines, horizontal forehead lines, and crow's feet has been well documented.^{1,2,11–13}

Furthermore, additional data have demonstrated progressive improvement in facial wrinkles with long-term use.^{14,15} This ongoing success has led physicians to increasingly incorporate botulinum toxin as an aesthetic treatment of the lower face,^{3,16} including hyperdynamic perioral lines (POLs).¹⁶

Despite growing interest in treating these areas, few published clinical studies exist that explore the optimal dose for botulinum toxin type A (BoNTA).^{16,17} The purpose of this study was to compare the safety, efficacy, and dose-response relationship of two doses of onabotulinumtoxinA in women with hyperdynamic POLs.

Methods

Study Design

This study was a multicenter, randomized, double-blind, parallel-design, dose-ranging trial in which subjects were randomized in a 1:1 ratio to receive 7.5 U of onabotulinumtoxinA (2 sites per lip: 5.0 U upper lip; 2.5 U lower lip) or 12.0 U onabotulinumtoxinA (2 sites per lip: 8.0 U upper lip; 4.0 U lower lip). OnabotulinumtoxinA was reconstituted in preserved saline. The volume of reconstituted toxin in each syringe was 0.30 mL to maintain the blind. Injection sites are shown in Figure 1. After the baseline visit (week 0), subjects returned for follow-up assessments at weeks 2, 4, 8, 12, 16, and 20 (visits 2–7). Investigators and subjects assessed POL severity and lip satisfaction at all visits. Treatment responders were those achieving a reduction of at least 1 point on the investigator assessment of POL severity scale (maximum contraction) at week 4.

Inclusion criteria included women of any race aged 25 to 60 with a POL score of 2 or 3 (moderate or severe) at maximal attempted muscle contraction based on a 4-point scale that considered the upper and lower lips. Subjects agreed not to undergo facial cosmetic procedures during the study period. Prospective

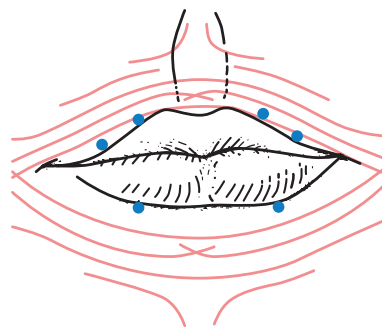


Figure 1. Sites of onabotulinumtoxinA injections. Equal doses were injected at all sites in a patient. (Adapted with permission from Gray H. *Anatomy of the Human Body*. 1918; Bartleby.com, Inc.).

subjects were excluded from study participation if they had undergone prior cosmetic surgery or exhibited facial scars that may have affected evaluation of response or the quality of photography. Other important exclusion criteria were asymmetric line severity between the upper and lower lips; imprinted etched-in lines at rest in the perioral area; the presence of facial hair affecting the evaluation of response or quality of photography; injection of nonpermanent lip filler into the perioral area in the 18 months preceding visit 1; previous botulinum toxin therapy in the mid or lower face within the 12 months preceding visit 1; previous permanent procedure or treatment in the lower face; any medical condition or use of concurrent medication that might increase their risk of exposure to botulinum toxin medical or psychiatric problems that, in the investigator's opinion, were severe enough to interfere with the study results; or allergy or sensitivity to any component of the study medication.

Good Clinical Practice

This study was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the Declaration of Helsinki. Informed consent was obtained from all subjects before participation in any study-related procedures.

Assessments of Efficacy

The primary efficacy variable was investigator-assessed POL severity scale at maximal contraction.

Although the upper and lower lips were both treated because of subject preference for consistent look of both lips, only the upper lips were evaluated for efficacy. The investigator assessed subjects' upper lip POLs at maximal contraction using the 4-point scale (0 = none, no lines; 1 = mild, few shallow lines; 2 = moderate, some moderate lines; 3 = severe, many deep lines or crevices). Secondary efficacy variables included investigator-assessed POLs at repose and subject-assessed POLs at maximum contraction and repose, both based on the same scales as their respective primary efficacy measures. The investigator also completed the Investigator Lip Satisfaction Questionnaire total lip satisfaction score (ILS-TS), a composite sum of the answers to seven questions that measure lip satisfaction. Each of these questions is given a score from a 5-point scale: -2 = very dissatisfied, -1 = dissatisfied, 0 = neither satisfied nor dissatisfied, 1 = satisfied, 2 = very satisfied. The range of the total score is -14 to 14: 7 questions on a scale of -2 to +2.

Facial Photography and Measurements

Facial photography was performed at all study visits, during repose and at maximal contraction, using a Canfield photography system (Canfield Imaging Systems, Fairfield, NJ), which provides high-resolution facial photography and ensures reproducibility of images between time points under standardized lighting conditions. Vertical lip length was measured from commissure to vermilion border and horizontal lip margin to control image size.

Safety Assessments

Determination of adverse events (AEs) was based on investigator assessments and subject reports of signs and symptoms, as well as physical examinations. Throughout the study, subjects were monitored for signs and symptoms of AEs.

Statistical Analyses

Statistical analyses of all enrolled subjects were conducted on an intention-to-treat basis. All

statistical testing was two-sided, and all analyses were interpreted at an alpha of 5% ($p < .05$). Subject questionnaires were analyzed between groups using chi-square tests. Descriptive statistics (mean and standard deviation) were determined according to treatment group for all continuous variables. Frequencies were reported for all categorical variables. Comparisons between treatment groups were performed using an analysis of covariance technique with the baseline value as the covariate. The Wilcoxon rank-sum test was used when the necessary assumptions for parametric tests were not satisfied. The Wilcoxon signed-rank test was used for within-group comparisons for POLs, lip satisfaction, self-perception of age, and subject self-evaluation. Safety analyses were performed based on incidence and severity of adverse or unexpected events.

Results

Overall, 60 women with a mean age of 41.9 ± 8.0 were randomized to onabotulinumtoxinA 12.0 U ($n = 29$) or 7.5 U ($n = 31$). Fifty-one subjects (85%) completed the study, of whom 26 and 25 subjects were from the 12.0-U and 7.5-U arms, respectively. Baseline demographics and characteristics are presented in Table 1.

Investigator Assessments of Efficacy

Investigator-assessed mean POL severity decreased significantly from baseline through week 20 for the 12.0-U dose ($p < .01$) and through week 16 for the 7.5-U dose ($p < .05$) (Figure 2). Responder rates were not significantly different between the two groups until week 12 (12.0 U, 77%; 7.5 U, 36%; $p = .003$; Figure 3). Unretouched representative photographs of subjects treated with 7.5 and 12.0 U onabotulinumtoxinA are provided in Figure 4.

There were no dose differences in investigator assessment of lip satisfaction overall appearance (ILS-OA) at any time point. Satisfaction was highest 2 weeks after treatment for the 7.5-U (93%) and

TABLE 1. Subject Demographics and Characteristics

	Total (N = 60)	OnabotulinumtoxinA 7.5 U (n = 31)	OnabotulinumtoxinA 12.0 U (n = 29)
Age, mean ± SD	41.9 ± 8.0	40.8 ± 7.1	43.2 ± 8.7
Race, n (%)			
Caucasian	54 (90.0)	30 (96.8)	24 (82.8)
Black	3 (5.0)	1 (3.2)	2 (6.9)
Hispanic	3 (5.0)	0 (0)	3 (10.3)
Total injected volume, mL, mean ± SD	0.30 ± 0.00	0.30 ± 0.00	0.30 ± 0.00
Subject disposition: completed study to week 20, n (%)	51 (85.0)	25 (80.6)	26 (89.7)

SD = standard deviation.

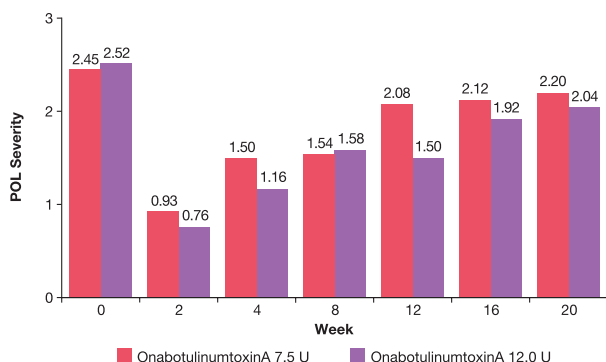


Figure 2. Investigator-assessed mean perioral line (POL) severity at maximum contraction. Mean POL severity decreased significantly from baseline through week 20 for 12 U ($p < .01$). Significant POL reduction for 7.5 U persisted until week 15 ($p < .05$). POL severity: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

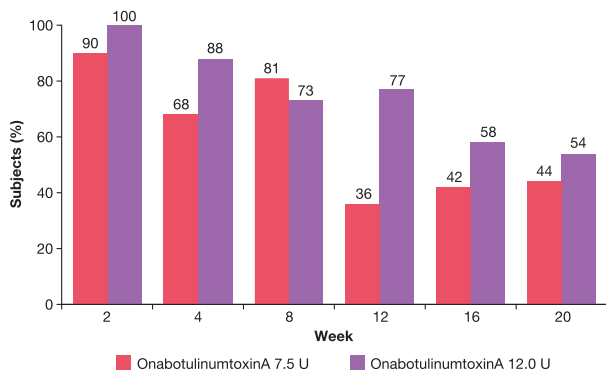


Figure 3. Investigator-assessed responder rate. *Subjects with reduction of at least 1 point in perioral line (POL) severity. †Significant differences were detected at week 12 ($p = .003$). POL severity: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

12.0-U (97%) doses and ranged between 69% and 89% for all other time points, although satisfaction was higher for the 7.5-U dose (84%) than the 12.0-U dose (73%) at 20 weeks. The effects of muscle softening led to significant changes in ILS-OA from baseline for the 7.5-U and 12.0-U doses at week 2 ($p < .05$). ILS-TS improved significantly from baseline to weeks 2, 4, 16, and 20 for the 12.0-U dose ($p < .05$) and to weeks 2, 16, and 20 for the 7.5 U-dose ($p < .05$). Total scores peaked at week 2 and for the 7.5-U (6.21 ± 3.28) and 12.0-U (7.0 ± 3.68) doses, and both doses demonstrated a general tapering until week 20.

Subject Assessments of Efficacy

Subject-assessed lip satisfaction overall appearance (SLS-OA) improved from baseline at all time points for the 7.5-U and 12.0 U-doses. For both doses, satisfaction peaked at week 8 (7.5-U, 73%; 12.0-U, 81%). Satisfaction with 7.5 U was greater at weeks 2, 12, 16, and 20 (Figure 5A,B). Mean subject-assessed lip satisfaction total score (SLS-TS) improved significantly from baseline ($p < .05$) to all time points for both groups, except at week 20 (12.0 U; $p = .06$). The change from baseline in SLS-TS was significantly greater all time points for the 7.5-U dose and up to 16 weeks for the 12.0-U dose ($p < .05$; Figure 6). Between-group differences were not statistically significant at any time point.



Figure 4. Unretouched representative photographs of subjects treated with onabotulinumtoxinA (A) 12.0 U, (B) 7.5 U.

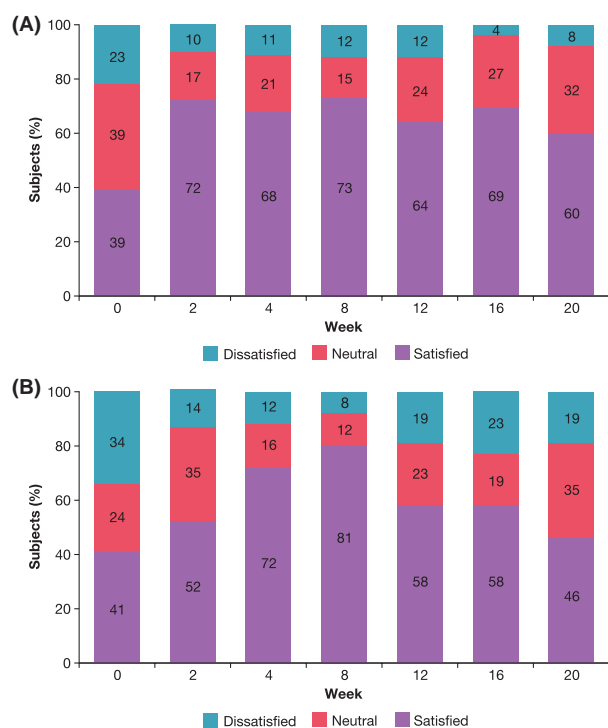


Figure 5. Subject-assessed lip satisfaction, overall appearance, of onabotulinumtoxinA (A) 7.5 U, (B) 12.0 U. Dissatisfied is the sum of very dissatisfied and dissatisfied, neutral is the number of neither satisfied or dissatisfied; satisfied is the sum of satisfied and very satisfied. Overall appearance corresponds to question 1 of the lip satisfaction questionnaire. -2 = very dissatisfied, -1 = dissatisfied, 0 = neither satisfied nor dissatisfied, 1 = satisfied, 2 = very satisfied.

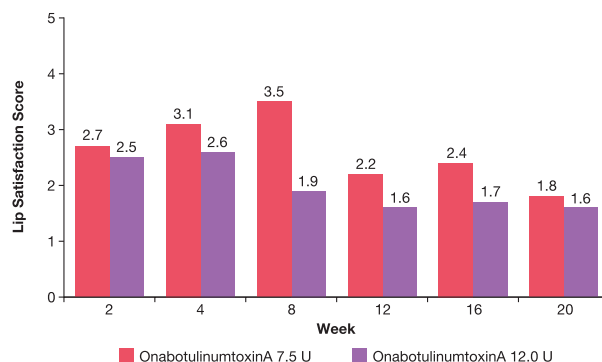


Figure 6. Subject-assessed lip satisfaction, total score change from baseline. Subject-assessed total lip satisfaction was significantly greater at all time points for 7.5-U dose and up to 16 weeks for 12.0-U dose. Total lip satisfaction score: composite sum of all seven lip satisfaction questions (range -14 to +14): -2 = very dissatisfied, -1 = dissatisfied, 0 = neither satisfied nor dissatisfied, 1 = satisfied, 2 = very satisfied.

Safety Assessments

Most AEs were mild to moderate in severity and were resolved without additional follow-up (Table 2). Most AEs were typical for treatment with BoNTA in the lips, and the rate of occurrence was dose-dependent. Representative treatment-related AEs (TRAEs) included weakness of the lips, numbness, trouble eating, lip dryness, lip fullness, and lip

TABLE 2. Summary of Adverse Events (AEs)

	Total (N = 59)	OnabotulinumtoxinA 7.5 U (n = 30)	OnabotulinumtoxinA 12.0 U (n = 29)
AEs, n (%)	35 (59.3)	14 (46.7)	21 (72.4)
Events	87	39	48
p Value (chi-square)	.04		
Serious AEs, n (%)	0 (0)	0 (0)	0 (0)
Events	0	0	0
Treatment-related AEs (definite/probable), n (%)	31 (52.5)	13 (43.3)	18 (62.1)
Events, n/N (%)	59/87 (67.8)	27/39 (69.2)	32/48 (66.7)
p Value (chi-square)	.15		

TABLE 3. Duration of Treatment-Related Adverse Events (TRAEs)

Resolved Within	OnabotulinumtoxinA 7.5 U n (%)	OnabotulinumtoxinA 12.0 U n (%)
≤ 7 days	12 (38.7)	7 (20.6)
8–21 days	15 (48.4)	9 (26.5)
22–50 days	4 (12.9)	3 (8.8)
51–113 days	0 (0)	10 (29.4)
Required follow-up*	0 (0)	5 (14.7)

Only subjects with at least one postbaseline visit or who reported AEs were taken into account.

*Mild to moderate TRAEs requiring follow-up, which was ongoing at study termination.

swelling. For the 7.5-U dose, all TRAEs except one (inability to kiss) were mild to moderate in severity, and all resolved without sequelae. For the 12.0-U dose, all TRAEs except one (decreased mobility of lips) were mild to moderate in severity. Most TRAEs resolved without follow-up. At the conclusion of the study, follow-up continued for dryness of the lips, influenza-like syndrome, bruising of the left upper lip, and decreased mobility of the mouth in two subjects. The duration of TRAEs are reported in Table 3.

Discussion

Because onabotulinumtoxinA is not approved to treat the lips or perioral area, doses for the treatment of hyperdynamic POLs have previously been based on clinical experience.¹⁷ This study demonstrates that treatment with onabotulinumtoxinA in 7.5-U and 12.0-U doses yields significant reductions in investigator-assessed POL severity for 16 and 20 weeks, respectively. Significant differences

between treatment groups in investigator-assessed responder rates (subjects with reduction of at least a 1 point in POL severity) were reported only at week 12, suggesting that the duration of effectiveness was not dose dependent. The responder rate for the 7.5-U dose increased at weeks 16 and 20. As such, these findings clearly support the efficacy of 7.5- and 12.0-U dose regimens for the reduction of hyperdynamic POL severity.

Throughout the study, subjects reported satisfaction with the outcomes achieved with the 7.5- and 12.0-U doses. Lip satisfaction total score improved significantly at most time points for both doses. SLS-OA for both doses peaked at 8 weeks, 73% for the 7.5-U dose and 81% for the 12.0-U dose. Similar to the assessments of efficacy, dose dependence was not demonstrated for these measures.

ILS-TS was also consistent, with a lack of dose response, although ILS-OA was high throughout the study, with the highest satisfaction 2 weeks after

treatment for the 7.5- (93%) and 12.0-U (97%) doses, and ranged between 69% and 89% for all other time points. Thus, patient satisfaction was not dose dependent and appears to justify the use of the lowest possible dose.

Because of the lack of clear dose response and the higher frequency of AEs with the higher dose, conservative treatment of hyperdynamic POLs with onabotulinumtoxinA 7.5 U may be sufficient in most cases, although the data do not preclude the use of 12.0 U to accommodate individual patient needs.

A conservative approach is typically taken when administering aesthetic treatments to the lower face. The approach to perioral treatment has become more measured than that practiced in previous years. In the 2008 Consensus Recommendations,¹⁸ perioral dosages were revised to 4.0 to 5.0 U from the 4.0 to 10.0 U that had been recommended in the 2004 Consensus Recommendations.¹⁹ In general, patients seeking BoNTA treatment typically fall into two categories. The first category includes those exhibiting visible lines during facial animation. These patients can benefit from onabotulinumtoxinA monotherapy. Based on data from the current study, injectors should now be aware that, even with a 7.5-U dose of onabotulinumtoxinA, the typical 3- to 4-month duration can be achieved, even in the highly active perioral musculature. The second category of patients includes those exhibiting etched-in lines at rest. These patients are best treated using a combination approach. Consensus guidelines have been developed to reflect such combination use.¹⁸ Recent studies have provided evidence of efficacy and patient satisfaction with combination treatment in the lower face.^{20,21} Various studies have shown that pretreatment with onabotulinumtoxinA is synergistic with hyaluronic acid fillers to provide longer-lasting results²² and better results with broadband light²³ or with chemabrasion (chemical peel plus dermabrasion).²⁴ The use of lower-dose onabotulinumtoxinA in conjunction with other treatment modalities provides for more-synergistic improvement; reduces the likelihood of

AEs and overreliance on any one modality; and it is hoped, delays the long-term etching of lines similar to hyperfunctional glabellar muscles.

The findings of this study suggest the possible frequency of retreatment with onabotulinumtoxinA while undergoing a typical sequence of aesthetic procedures. For example, approximately three fractionated laser treatments may be performed between onabotulinumtoxinA treatments.^{22,25} This strategy may lead to greater improvement because there will be less muscle contraction across the healing wound of the laser. If fillers are used in conjunction with onabotulinumtoxinA treatments, the durability of fillers placed within etched-in lines or areas of volume loss will also be greater when onabotulinumtoxinA is administered at these intervals in the perioral area.

The primary limitation of this study was the selection and availability of two dosing regimens. The intent of this study was to compare a commonly used dose of 7.5 U with a higher dose of 12.0 U. Because patients present with a wide spectrum of wrinkle severity, some may be successfully treated with as little as 5.0 U, whereas others with more-prominent POLs may require 10.0 U or more.

Unlike the glabellar complex, assessment of muscle mass and patient response in the perioral area can be difficult, and the use of larger doses in the perioral area can be a clinical limitation. Therefore, before undertaking treatment of hyperdynamic POLs, injectors should be aware of the challenges they may encounter in the lower facial area to avoid potential undesired effects on perioral function.

The consideration of dose is critically important for injectors. In the perioral region, muscular immobilization is not a desirable outcome; rather, weakening of the perioral musculature to prevent pursing and formation of lines is the expected endpoint. Impairment of the ability to kiss, phonation, or drinking from supraoptimal dosing may adversely influence the patient's perception of treatment

outcomes. It is advisable to initiate with lower doses until the injector and patient have had the opportunity to evaluate treatment response. When treating the perioral region, it is essential to educate the patient that the posttreatment differences compared with the glabella will be more subtle but are to be expected and will indicate a successful outcome. Favorable treatment of the glabellar area is achieved by immobilization of the procerus and corrugator complex. This is not the case in the perioral area; weakening of the muscles without impairing function is the goal. Development of scales to rate treatment outcomes (as in this study), establish patient expectations, and provide patient education is warranted.

Conclusions

The study confirms that treatment of hyperdynamic POLs using onabotulinumtoxinA results in significant reductions from baseline in POL severity and high levels of patient satisfaction. Treatment with onabotulinumtoxinA 7.5 U appears adequate. Although a total dose of 12.0 U has the potential for greater AEs, it may provide a longer duration of correction in some patients. It is likely that these data will facilitate more-informed decisions on the preferred onabotulinumtoxinA dose and deepen the understanding of optimal treatment intervals when combination or multimodal facial treatments are desired.

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