Aesth Plast Surg (2008) 32:715–722
DOI 10.1007/s00266-008-9151-9

ORIGINAL ARTICLE

# Novel Topical BoNTA (CosmeTox, Toxin Type A) Cream Used to Treat Hyperfunctional Wrinkles of the Face, Mouth, and Neck

**I. Chajchir · P. Modi · A. Chajchir**

Received: 30 October 2007 / Accepted: 10 November 2007 / Published online: 15 May 2008


**Abstract**
*Background* This study aimed to compare the effect of the stabilized novel topical botulinum neurotoxin type A (BoNTA) cream (CosmeTox) and a placebo cream on subjects, to compare clinician-reported outcomes, and to assess the safety and utility of the novel topical BoNTA cream for treating the entire upper face, chin, and neck areas.
*Methods* This study randomized 40 female subjects to receive either topical BoNTA (CosmeTox) cream (2 U/ml) or an identical placebo cream (without BoNTA) on the face, chin, and neck areas. The subjects were followed for 12 weeks. The main outcome measures were the Facial Line Outcomes questionnaire scores and results from the Self-Perception of Age instrument, which assesses age of appearance relative to actual age.
*Results* The BoNTA topical cream (CosmeTox) treatment produced significant improvements in the Facial Lines Outcome scores, which were maintained throughout the study period and lasted more than 3 months. The BoNTA topical cream treatment also reduced the age of appearance for a majority of subjects. The placebo had no effect on any measure. No serious adverse events occurred during the entire study period.
*Conclusion* Topical treatment with the stabilized BoNTA cream (CosmeTox) to the entire upper facial lines resulted in significantly improved facial features and age appearance, as measured by the subjects and clinicians. The BoNTA cream (CosmeTox) resulted in a significantly younger, more satisfying, relaxed appearance.

**Keywords** Aesthetics medicine · Botulinum toxin-A (BoNTA) · BoNTA-topical cream · CosmeTox · Facial lines · Mouth · Neck

I. Chajchir (✉) · A. Chajchir
Cirugia Plastica Estetica, Centro Medico Barrancas, Joes Hernandez 1718(C1426DZE), Buenos Aires, Argentina
e-mail: irina.chajchir@fibertel.com.ar

P. Modi
DPM Therapeutics Corporation, Ancaster, Ontario, Canada

Facial lines and wrinkles have a multifactorial etiology including sun exposure, loss of dermal elastic fibers, skin atrophy, and excessive muscle activity. Hyperkinetic wrinkles result from recurring contraction of the muscles, producing expression in the face and neck. Hyperfunctional facial lines are distressing to patients because they often are misinterpreted as anger, fear, fatigue, melancholia, and aging. They represent a prevalent clinical scenario. Patients often look to aesthetics medicine for resolution [1–13].

Botulinum toxin type A (BTX-A) has been used in cases of hyperkinetic wrinkles since 1987, when Carruthers and others noted the smoothing effect of botulinum neurotoxin type A (BoNTA) on facial lines and wrinkles. One of the earlier published reports on the aesthetic uses of BoNTA demonstrated that treatment of upper facial lines was highly effective in providing facial rejuvenation [2, 3, 16].

Botulinum toxin therapy produces a diminution of hyperfunctional facial lines and wrinkles. The ways that BoNTA is used in aesthetic medicine have evolved as clinical experience has expanded, and as the role of facial muscles in communication and emotional expression have become better appreciated [3–6]. Accordingly, current treatment strategies attempt to avoid a frozen look, to provide a more natural relaxed look, and to enhance overall facial appearance [3–4]. Consistent with this approach, many clinical practices treat mostly with BTX-A to smooth hyperkinetic lines in the periocular and forehead areas of

**Table 1** Potential complications

| Relative | Described | Rare |
|---|---|---|
| Pain | Eyelid ptosis | Allergy |
| Bruising | Eyebrow ptosis | Focal atrophy |
| Sensation of loss of strength | Fixed facial expression mask | Altered sweating |
| Discrete edema | Asymmetry | Antibody formation |
| Local infection | Functional alteration | Diplopia |

the upper face. Findings have shown BoNTA to be safe for the upper facial region [6, 9, 11–13].

Long-term exposure to toxin causes reversible denervation atrophy. Reinnervation occurs through noncollateral sprouting followed by repair of the docking protein that was cleaved. Clinically, the weakening effects of BoNTA last about 3 to 4 months.

The potential complications of BTX-A therapy can be characterized as relative, described, and rare, as shown in Table 1. *Relative* complications are avoidable or easily resolved. *Described* complications commonly occur but generally are not problematic for the patient or clinician. These complications can arise from errors in technique, patient selection, dilution, and dosing. They can result in eyelid or eyebrow ptosis, incompetent mouth, or facial asymmetry [15]. Of the *rare* complications, antibody formation is particularly undesirable because the development of neutralizing antibodies may lead to loss of effect from therapy.

Antibody formation occurs more often with BTX-A when there are frequent injections of doses with shorter intervals of 1 month or less between procedures and when accidental intravenous injections occur [14]. Thus, antibody formation is dose and frequency dependent [17]. For this reason, the lowest dose with proven efficacy is recommended, with a minimum of 3 months between procedures [5, 7].

Furthermore, not everyone will opt to have this painful injection therapy to correct their facial defects and improve their looks. The complications of toxin injections may lead to bruising or local pain related to the injection needle. There also may be weakness of adjacent muscles related to diffusion of the toxin. The amount of diffusion and weakness usually is related to incorrect or excessive doses.

One way to overcome the painful injections and the resistance factor is to start treatment with the novel topical formulation of BoNTA cream (CosmeTox) (small daily dose of 2 U/ml) for those who are needle phobic and do not want injections. Those who want to prolong the effect of Botox injections will use this cream (CosmeTox) after their injection treatments as maintenance therapy for a prolonged period to avoid or slow down the process of wrinkle formation. Our earlier preliminary studies have shown its effectiveness in reducing wrinkle formation, improving facial features, and reducing aging appearance in subjects with hyperfunctional lines and wrinkles.

Based on our clinical experiences and results, we conducted this study to assess the effects of the stabilized novel topical BoNTA cream (CosmeTox) or a placebo cream (without BoNTA) on female subjects with multiple upper facial rhytids (glabella, crow's feet, forehead, and neck) using clinician-reported outcomes and self-perception of age (SPA) assessments. Male subjects were not included in this study because the facial anatomy, aesthetic goals, and BoNTA dosage for men are different from those for women.

The minimal effective dose of the novel BoNTA topical cream was chosen to optimize outcomes without overtreating although it is inconsistent with dosage recommendations for each individual area of the upper face [5, 18].

## Materials and Methods

### Preparation of Topical BoNTA Cream (CosmeTox)

The procedure was performed using BoNTA (toxin-A allergan) diluted with 1 ml of saline solution without preservatives for each 100 U of the active product. The solution was stirred to mix and dispersed the BoNTA homogeneously. This homogenized solution was added to the cream base made using our proprietary InParT (ionic nanoparticle technology), followed by mixing and dispersion to obtain 2 U of BoNTA per milliliter of cream base. This stabilized BoNTA cream then was aliquoted (1-ml volume) in special plastic individual bubble packs (each 1 ml in size) and stored at room temperature for further use.

### Study Design

This single-center, single-blinded, parallel-group, prospective study involved 4 to 7 weeks of treatment and 12 weeks of follow-up evaluation. The study was a randomized comparison between the topical BoNTA cream (CosmeTox) treatment and a placebo cream, with follow-up visits every week for 12 weeks or more.

### Subjects

The study complied with the Declaration of Helsinki recommendations for biomedical research with human subjects. Institutional review board approval was obtained, and enrolled subjects provided written informed consent after the study design, purpose, and potential risks were

discussed. Female subjects of any race who were 35 to 65 years of age were eligible.

The subjects' upper facial rhytids were rated with the 4-point Facial Wrinkle Scale (FWS) as 0 (none), 1 (mild), 2 (moderate), or 3 (severe). For inclusion in the study, their maximum attempted frown, eyebrow elevation, or smile had to show moderate or severe glabellar lines, moderate or severe forehead lines, and bilaterally symmetric moderate or severe crow's feet (Tables 1–3)., as determined by a trained observer. The subjects had to be able to understand the requirements of the study, to comply and cooperate with those requirements, and to sign an informed consent form.

Subjects were not eligible for participation in the study if they were currently breastfeeding or had any disorder, condition, or circumstance that could potentially impair compliance with the study. Subjects with low brows and those with a probability of brow ptosis were excluded from the study. Those with childbearing potential had to have a negative urine pregnancy test result at the baseline visit and had to practice a reliable method of contraception throughout the study. Only subjects who had not received previous therapy with botulinum toxin of any serotype within 120 days of the baseline visit nor had participated in any other investigational within 120 days of the baseline visit were allowed to enter the study. The planned enrollment was 40 subjects, 20 per treatment group.

## Study Procedures

At the screening and the baseline visit (week 0), the subjects were asked to check into the clinic for assessment of hyperfunctional lines and wrinkles and to complete the Facial Lines Outcome (FLO) questionnaire and the SPA assessment. All the subjects were assessed for general health and well-being at the screening visit. The study nurse took a complete medical history and photographs of the forehead, the area around the eyes for crow feet, and in general, the whole face for any noticeable wrinkles when the subject was at rest and in motion at the beginning of the study and at every clinical visit thereafter. Enrolled eligible subjects were randomly assigned to receive either treatment with the novel stabilized BoNTA cream (2 U/ml) or with a placebo cream (without BoNTA).

Group 1 was treated with the topical BoNTA cream (2 U/ml) every evening (20 subjects), and group 2 was treated with the placebo topical cream (without BoNTA) every evening (20 subjects). The treatment was administered on an inpatient/outpatient basis for 4 to 7 weeks (42–49 days) to both groups. The sponsor of the study, DPM Therapeutics Corporation (Ontario, Canada), supplied the novel stabilized topical BoNTA cream formulation. The units of botulinum toxin-A in this report refer specifically to the novel cream formulation preparation and are identical to the units used in other preparations of botulinum toxin-A (Botox).

The subjects were asked to clean their faces well with specially formulated soap and warm water before treatment at the clinic and at home. The study nurse or doctor then applied the given doses of the novel topical BoNTA cream (2 U/ml) or the placebo cream formulation with gentle rubbing to ensure the proper penetration of the cream. The subjects were asked to sit in the clinic for about 30 to 45 min after their first treatment so any sign of irritation, burning, redness, or itchiness together with any other notable unusual feelings could be observed. All the subjects were photographed 30 to 45 min after their first treatment with the topical BoNTA cream or placebo and every week during their clinical visits.

The treatment procedure was continued (self-administered by the subjects at their home as instructed) for 4 to 7 weeks. The subjects were asked to return to the clinic once a week for 7 weeks for physical examinations, photographs, and assessment of reduction in their wrinkles. The total dose of the CosmeTox topical formulation administered per subject during this trial period was 50 to 70 U depending on the treatment duration because most of the subjects required only 5 weeks of treatment. Line severity using the FWS, physician global assessment of improvement, and subject-reported outcomes was assessed at each visit. Adverse events and concomitant medications also were assessed throughout the trial period.

On their last day of treatment with the BoNTA topical cream formulation (CosmeTox), the subjects were asked the following questions. Are you satisfied with this treatment (completely satisfied, satisfied, partially satisfied, or not satisfied)? How would you describe your tolerance of this treatment (excellent, good, fair, or poor)? Would you recommend this treatment to others (in all cases, in most cases, in some cases, or not at all)?

## Outcome Measures

Line severity was assessed during repose and at maximum attempted contraction using the FWS. The subjects rated improvement of their upper facial rhytids using the following 9-point Subjects' Global Assessment Scale: +4 (100% improvement), +3 (75% improvement), +2 (50% improvement), +1 (25% improvement), 0 (no change), −1 (25% worsening), −2 (50% worsening), −3 (75% worsening), −4 (100% worsening). The main subject-reported outcomes were FLO and SPA (Tables 2 and 3).

The FLO questionnaire measured subject-reported outcomes relevant to the treatment of hyperfunctional lines in the upper face (glabellar lines, horizontal forehead lines, and crow's feet). The items in the FLO questionnaire were

**Table 2** Subjects' global assessment (SGA) scale

Table 1. Subject's global assessment of treatment satisfaction scale

| Score | Description |
|---|---|
| +4 | Complete abolition of signs and aging symptoms (about 100% improvement) |
| +3 | Substantial improvement (some signs and symptoms remain, about 75% improvement) |
| +2 | Moderate improvement (definite improvement but a fair amount of signs and symptoms remain, about 50% improvement) |
| +1 | Slight improvement (some improvement but substantial signs and symptoms remain, about 25% improvement) |
| 0 | Unchanged |

**Table 3** The Global Aesthetic Improvement Scale

| Score | Description |
|---|---|
| 5 | Extreme: Extremely deep an long folds, detrimental to facial appearance. 2–4 mm visible V-shaped fold when stretched. |
| 4 | Severe: Very long and deep folds; prominent facial feature. Less than 2 mm visible fold when stretched. |
| 3 | Moderate: Moderately deep folds; clear facial feature visible at normal appearance but not when stretched. |
| 2 | Mild: Shallow but visible fold with a slight indentation; minor facial feature. Implant is expected to produce a slight improvement in appearance |
| 1 | Absent: No visible fold; continuous skin line |

derived from a combination of literature review, feedback from physician facial aesthetics experts, and personal interviews with subjects who completed the study with BoNTA topical cream for facial hyperfunctional lines.

The subjects rated the items in the FLO questionnaire according to their impressions after the first 2 weeks of cream use and every week thereafter throughout the study using the following 5-point scale: 0 (not at all), 1 (somewhat), 2 (mild), 3 (moderate), and 4 (significant improvement) (Tables 2 and 3). As a result, the subjects' scores from these items alone were analyzed in this study. Together, these items evaluated the extent to which subjects thought their facial lines bothered them by making them look older than they wished to look, detracted from their facial appearance, prevented them from having a smooth appearance, and made them look tired, stressed, or angry, when this was not how they felt.

The subjects also evaluated their perception of age over the entire study period using the single-item SPA, which asks subjects to indicate whether they look their current age, younger, or older and to provide the number of years younger or older. Adverse events were assessed for incidence, severity, seriousness, unexpectedness, and relationship to treatment.

Questionaire

1. Which areas were treated with topical BoNTA cream? A ( ) Forehead, B ( ) Glabella, C ( ) Eyes, D ( ) Mouth, E ( ) Neck, F ( ) Nasogenial furrow, G ( ) Nose
2. In which facial area(s) were results more exuberant with topical BoNTA cream treatment? A ( ) Forehead, B ( ) Glabella, C ( ) Eyes, D ( ) Mouth, E ( ) Neck, F ( ) Nasogenial furrow, G ( ) Nose
3. In which facial area(s) have you noticed differences since you started the treatment with topical BoNTA cream? A ( ) Forehead, B ( ) Glabella, C ( ) Eyes, D ( ) Mouth, E ( ) Neck, F ( ) Nasogenial furrow, G ( ) Nose
4. How long did it take for the result to begin to appear with topical BoNTA cream? A ( ) 1–3 days, B ( ) 3–5 days, C ( ) 5–10 days, D ( ) 10–15 days, E ( ) more than 15 days
5. How long did it take for the results to consolidate with topical BoNTA cream treatment? A ( ) 1–3 days, B ( ) 3–5 days, C ( ) 5–10 days, D ( ) 10–15 days, E ( ) more than 15 days
6. With topical BoNTA cream treatment, how long were the results sustained? A ( ) 1 month, B ( ) 2 months, C ( ) 3 months, D ( ) 4 months, E ( ) more than 5 months
7. Have you noticed any differences in your appearance, age, or skin since treatment with the CosmeTox (BoNTA) topical cream? A ( ) yes, B ( ) No
8. Compared with regular BoNTA injection, which therapy would you prefer if you had a choice? A ( ) Botox injection, B ( ) Topical BoNTA cream CosmeTox
9. Regarding the cosmetic treatment performed with topical BoNTA cream, do you feel A ( ) Satisfied, B ( ) Very satisfied, C ( ) Not satisfied
10. In your opinion, the effectiveness was A ( ) Good, B ( ) Very good, C ( ) Mild
11. Would you recommend this treatment to others? A ( ) To everyone, B ( ) In most cases, C ( ) In some cases, D ( ) Not at all
12. How would you describe your tolerance of this treatment? A ( ) Excellent, B ( ) Good, C ( ) Fair, D ( ) Poor
13. Would you volunteer again for this new therapy? A ( ) Yes, B ( ) No

Statistical Considerations and Data Analyses

The sample size of 20 subjects per group was based on an alpha level of 0.05, a power of 0.80, the assumption of a 10% dropout rate, and an expected difference of 20 points in mean FLO scores using 0 to 100 scoring between the BoNTA topical cream and the placebo cream groups. The

main efficacy outcomes were the mean FLO scores every week, the number of subjects who reported looking younger than their current age, the mean number of years younger, and the distribution of scores on the FWS. The main safety outcomes were the frequency and severity of adverse events or unexpected events.

Statistical analyses were performed on an intent-to-treat basis. Between-group differences were evaluated using the following statistical tests: chi-square or Fisher's exact test for frequency distributions of line severity, SPA responses, and subject's global assessments of improvement; the Wilcoxon rank sum test and rank analysis of covariance (ANCOVA) with the baseline value as the covariate for line severity; the two-sample *t*-test and ANCOVA with the baseline value as a covariate for mean FLO scores and mean change from baseline in FLO scores; and the Wilcoxon rank sum test for the mean number of years subjects thought they looked older or younger than their current age. In addition, the Wilcoxon signed rank test was used to test the within-group nonzero difference from baseline for the mean number of years that subjects thought they looked older or younger than their current age. All $p$ values less than 0.05 were deemed statistically significant for all comparisons. All tests were two-tailed.

## Results

At baseline, there were no statistically significant differences in mean age between the topical BoNTA cream and placebo treatment groups in terms of mean age ($49 \pm 5$ years), race, physical examination/medical history, wrinkle severity for any of the three facial areas during repose or maximum attempted contraction (glabellar repose, glabellar maximum attempted contraction, crow's feet during repose, crow's feet maximum during attempted contraction, forehead during repose, forehead during maximum attempted contraction, or perceived age from appearance). All 40 subjects completed the study.

### Facial Line Outcomes

After 1 week of treatment, the mean FLO scores differed significantly between the novel topical BoNTA cream–treated subjects and placebo cream–treated subjects. The most active group treatment subjects reported significant improvements in their appearance and aging process within the first 2 weeks of treatment. The improvements in mean FLO scores were maintained by the topical BoNTA cream–treated subjects for the entire duration of the study (week 12). Preliminary assessment of the psychometric properties of the FLO questionnaire from this study indicated that it has acceptable test–retest reliability (Pearson correlation, 0.90 between screening and baseline) and internal consistency reliability. In addition, the FLO questionnaire demonstrated construct validity, with moderate to strong correlations with the subject-rated SPA item at baseline and after treatment visits, and with the investigator-rated FWS during both repose and maximum muscle contraction at weeks 2 and 4 after treatment visits. Most subjects in the active treatment group had significantly improved FLO and SPA scores.

### Self-Perception of Age

At baseline, the distribution of subjects who reported looking their current age, younger, or older did not differ significantly between the two groups. All topical BoNTA cream (CosmeTox)–treated subjects reported looking younger than their current age by a mean of 5 and 7 years, respectively. In contrast, the placebo cream–treated subjects observed no significant differences in before and after photographs. At weeks 2 to 4, less than 75% of the BoNTA cream–treated subjects reported looking younger than their current age, and this percentage was maintained through the 12 weeks of the study. Age perception also did not change among the placebo-treated subjects.

The mean difference between younger current age and perceived age at baseline was $5 \pm 2$ years for the BoNTA group and $7 \pm 2$ years for the placebo group. Changes from baseline in the mean number of years older or younger differed significantly between the groups as well as within the BoNTA-treated group. Statistically significant differences between the groups appeared as early as week 2 (or earlier) when the mean change from baseline was $3 \pm 3$ years younger for the BoNTA cream–treated group and $0.15 \pm 1$ years (no significant change) for the placebo group. At week 4, the mean change from baseline was $5 \pm 2$ years younger for BoNTA-treated subjects compared with $0.15 \pm 0.37$ years younger for the placebo group. In addition, statistically significant reductions from baseline in age of appearance were maintained through week 12 in the BoNTA topical cream–treated group. The responses to SPA at screening and baseline were well correlated, indicating test–retest reliability of this item.

### Facial Wrinkle Scale

No statistically significant differences in the frequency distribution across FWS scores occurred at baseline (at the beginning of the study period) for any facial area during either repose or maximum attempted contraction. At week 2, significantly greater percentages of subjects receiving BoNTA had FWS scores of 2+ or less compared with placebo-treated subjects (glabellar repose and crow's feet during repose, $p \leq 0.0003$; all other comparisons,

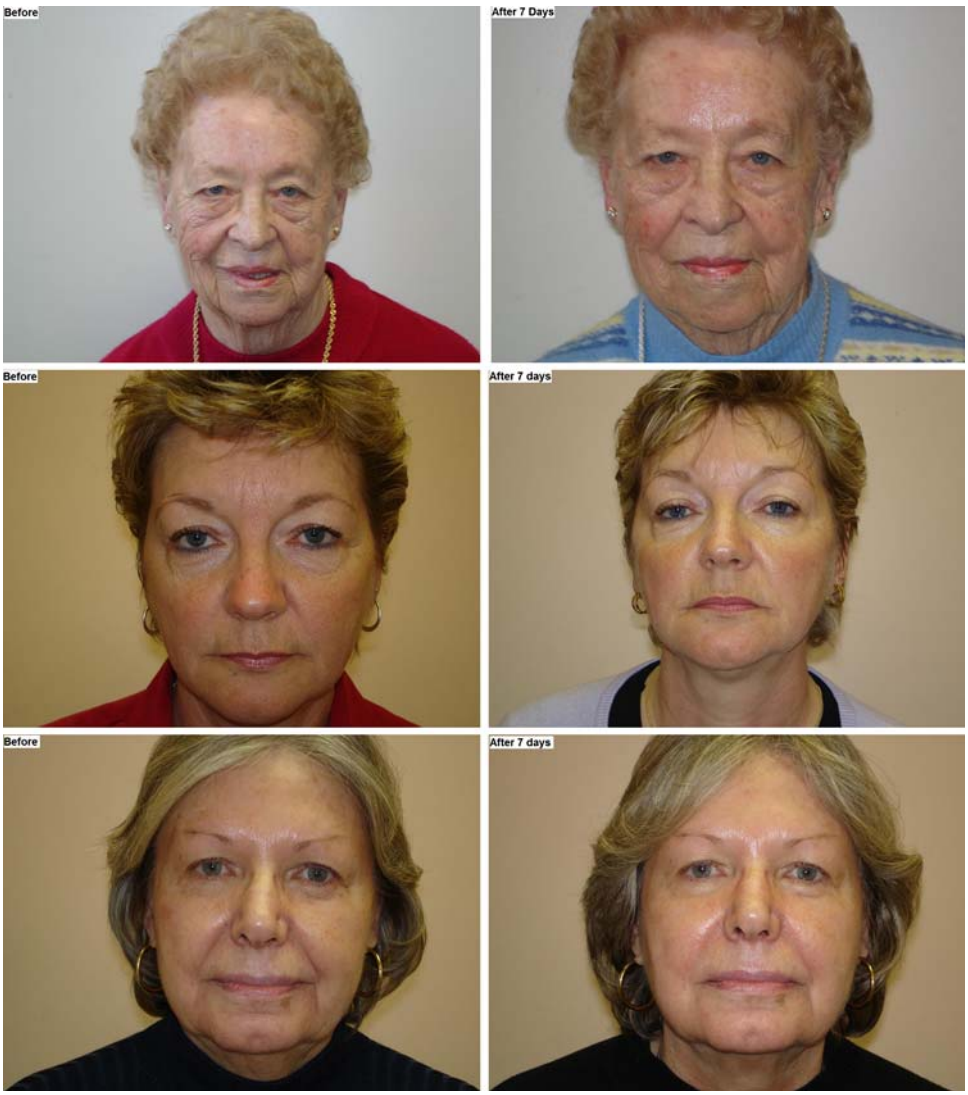


**Fig. 1** Pre- and post-treatment subjects

$p < 0.0001$). These differences were observed consistently in all visual contractions and frowns and in photographs. In the BoNTA cream–treatment group, the vast majority of subjects maintained scores of 2+ or less throughout the 12 weeks of the study. No significant differences were observed in the placebo group.

Most of the subjects treated with topical BoNTA cream reported significant overall improvements in their facial features, including fading of the dark circles under their eyes and hyperpigmentation reductions, as seen from the before and after photographs.

### Subjects' Global Assessment

At 2 weeks after their topical cream treatment, 100% of the BoNTA-treated subjects rated their rhytids as at least 25% to 50% improved compared with none of the placebo-treated subjects, a statistically significant difference ($p < 0.0001$). At week 4, more than 85% of the BoNTA cream–treated group rated their rhytids as improved by at least 75% or more. Sample images of subjects from the BoNTA group are shown in Figs. 1–3.

### Adverse Events

During the masked phase, three adverse events (a tight feeling across forehead, pulling lines on the upper outer eyelids, and dryness of the area treated with BoNTA cream) were considered probably or definitely related to treatment and occurred for most subjects in the BoNTA-treated group. All adverse events were transient and mild to moderate in severity. None were serious, and no ptosis occurred.

## Discussion

The study results confirm and extend our previous findings that the novel topical BoNTA cream (CosmeTox)

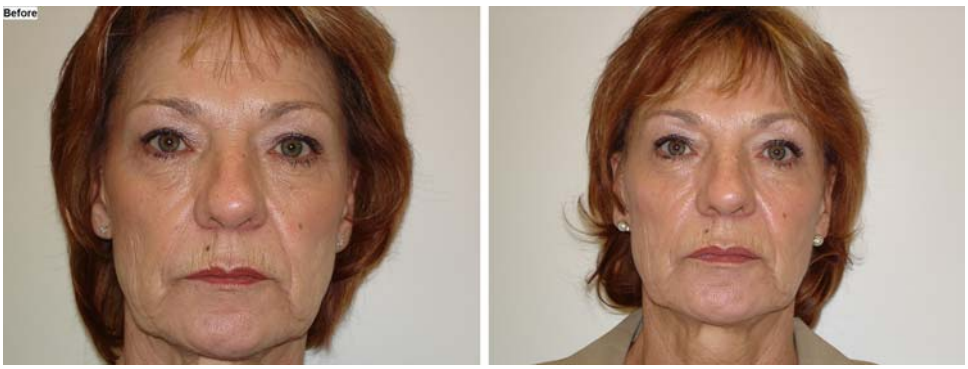


**Fig. 2** Subject before treatment and 7 days after treatment


**Fig. 3** Subject before treatment and 7 days after treatment

treatment for facial rhytids resulted in the younger, more relaxed appearance that patients desire when seeking treatment with BoNTA. This is consistent with evolving aesthetic goals of delivering pain-free, needle-free treatment and a more natural appearance to patients selecting treatment with BoNTA.

In this study, the 50 to 75 units of BoNTA used to treat multiple upper facial rhytids resulted in significant changes on the FLO questionnaire. The subjects reported improvements in the extent to which their facial lines bothered them, made them look older than they wished to look, detracted from their facial appearance, prevented them from having a smooth appearance, and made them look tired, stressed, or angry, even when they were not.

The BoNTA treatment also increased the proportion of subjects who reported looking younger than their current age, whereas the placebo had no effect on age perception or on the overall improvement in appearance. Throughout the study, 100% of the BoNTA cream–treated subjects reported looking younger. At 2 to 4 weeks after treatment, the BoNTA cream–treated subjects reported looking younger by 3 to 5 years compared with the perceived age at the baseline. Similar results were obtained in our previous studies (unpublished results) on treating areas of the face. The findings showed BoNTA as efficacious and well tolerated in reducing the severity of multiple facial rhytids, as measured by the FWS. Benefits were maintained throughout the duration of the study, which is important for subjects.

The limitations of this study included its relatively short duration (treatment period of 7 weeks or less). Longer studies would provide more information on the duration BoNTA's effect in treating the entire upper face. In addition, a fixed low dose of BoNTA cream was used, and no adjustments were allowed, in contrast to actual clinical practice, in which the dosing can be tailored to the individual's needs. Future research will be conducted to examine the effects of individually adjusted doses of BoNTA, to explore longer durations of treatment, and to further validate the FLO questionnaire, including test–retest reliability, construct validity, and minimally important (clinically significant) differences in FLO scores.

## References

1. Carruthers A, Carruthers J (1998) History of the cosmetic use of botulinum A exotoxin. Dermatol Surg 24:1168–1170
2. Carruthers J, Carruthers A (1998) The adjunctive usage of botulinum toxin. Dermatol Surg 24:1244–1247
3. Heckmann M, Teichmann B, Schroder U et al (2003) Pharmacologic denervation of frown muscles enhances baseline expression of happiness and decreases baseline expression of anger, sadness, and fear. J Am Acad Dermatol 49:213–216
4. Finn JC, Cox SE, Earl ML (2003) Social implications of hyperfunctional facial lines. Dermatol Surg 29:450–455
5. Carruthers J, Fagien S, Matarasso SL, Botox Consensus Group (2004) Consensus recommendations on the use of botulinum toxin type A in facial aesthetics. Plast Reconstr Surg 114(Suppl):1S–22S

6. Fagien S (2003) Botulinum toxin type A for facial aesthetic enhancement: role in facial shaping. Plast Reconstr Surg 112(Suppl):6S–18S
7. Carruthers JA, Lowe NJ, Menter MA et al (2002) A multicenter, double-blind, randomized, placebo-controlled study of the efficacy and safety of botulinum toxin type A in the treatment of glabellar lines. J Am Acad Dermatol 46:840–849
8. Carruthers A, Carruthers J, Cohen J (2003) A prospective, double-blind, randomized, parallel-group, dose-ranging study of botulinum toxin type A in female subjects with horizontal forehead rhytides. Dermatol Surg 29:461–467
9. Carruthers A, Carruthers J (2007) Foreword to special issue on botulinum toxin. Dermatol Surg 33:S1–S1
10. Carruthers A, Carruthers J (2007) Botulinum toxin type A treatment of multiple upper facial sites: patient-reported outcomes. Dermatol Surg 33:S10–S17
11. Fagian D, Cox SA, Finn J, Werscheller W, Kowalski J (2007) Patient-reported outcomes with botulinum toxin Type A treatment of glabellar rhytids: a double-blind, randomized, placebo-controlled study. Dermatol Surg 33:S2–S9
12. Rzanzy B, Dill-Muller D, Grablowicz D, Heckmann M, Caird D (2007) On behalf of the German–Austrian Retrospective Study Group, repeated botulinum toxin A injections for the treatment of lines in the upper face: a retrospective study of 4,103 treatments in 945 patients. Dermatol Surg 33:S18–S25
13. Singh G, Kelly M (2003) Botox an "elixir of youth"? Eur J Plast Surg 26:273–4
14. Markey AC (2000) Botulinum A exotoxin in cosmetic dermatology. Clin Exp Dermatol 25:173–175
15. Carruthers A, Carruthers J (1998) Clinical indications and injection technique for the cosmetic use of botulinum A exotoxin. Dermatol Surg 24:1189–1194
16. Garcia A, Fulton JE Jr (1996) Cosmetic denervation of the muscles of facial expression with botulinum toxin: a dose–response study. Dermatol Surg 22:39–43
17. Benedetto AV (1999) The costmetic uses of botulinum toxin type A. Int J Dermatol 38:641–655
18. Carruthers A, Carruthers J, Lowe NJ et al (2004) One-year, randomised, multicenter, two-period study of the safety and efficacy of repeated treatments with botulinum toxin type A in patients with glabellar lines. J Clin Res 7:1–20