

Three-Dimensional Evaluation of Static and Dynamic Effects of Botulinum Toxin A on Glabellar Frown Lines

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Abstract

Background The use of injectable solutions for aesthetic purposes has increased tremendously, but lacks objective support. We aimed at assessing static and dynamic effects of botulinum toxin A (BoNTA) on glabellar lines by use of an objective three-dimensional methodology.

Methods We prospectively collected three-dimensional stereographic photographs of two different facial expressions (pretreatment, 30 and 90 days posttreatment) in 21 patients, receiving a total of 20 units of BoNTA in both corrugator supercillii muscles. The primary endpoint was the three-dimensional static and dynamic surface irregularity, and secondary endpoints were the glabellar line scale and overall patient satisfaction. Blinded retrospective data analysis and statistical evaluation were performed with $p < 0.05$ considered statistically significant.

Results Static glabellar lines (neutral facial expression) were significantly reduced by -17% and -24% on day 30 and 90 posttreatment, respectively (vs. pretreatment; both $p < 0.0001$). Dynamic glabellar frown lines (firmest possible bilateral eye closure) demonstrated a reduction of surface irregularity by -26% and -21% on day 30 and 90 posttreatment, respectively (vs. pretreatment; both

$p < 0.0001$). The subjective dynamic glabellar line scale documented a statistically significant improvement on day 30 posttreatment (mean \pm SD: 1.5 ± 0.8 ; $p < 0.05$) versus pretreatment (2.8 ± 1.0). Polled patients confirmed a subjective wrinkle improvement 90 days posttreatment.

Conclusion The presented setup detected even subtle changes of BoNTA treatment for facial wrinkling and is a promising asset for scientific evaluations of clinical studies analyzing the outcome and duration of efficacy of injectable solutions on the face.

Level of Evidence IV This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266.

Keywords Rejuvenation · Facial · Botox · Objective · Three-dimensional

Introduction

The US Food and Drug Administration (USFDA) approved BoNTA for the treatment of glabellar lines (GL) [1] and crow's feet [2] in 2002 and 2013, respectively. The annual use of botulinum toxin injections for cosmetic purposes has increased by 748% over the past 14 years [3]. In 2014 botulinum toxin type A (BoNTA) accounted for up to 6.7 million performed treatments throughout the USA [3]. BoNTA is the leading minimally invasive substance used for facial rejuvenation, twice as much as compared to soft tissue fillers. Both are often used in combination [4]: soft tissue fillers for volume corrections and BoNTA for muscular blockade; the focus of this work is aimed at the dynamic and static changes induced by BoNTA.

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The so far registered (clinicaltrials.gov) and published cosmetic BoNTA studies lack an objective support. Only two studies [5, 6] used objective tools to assess BoNTA treatments in the upper face. Subjective assessments as performed by the use of the Facial Wrinkle Scale, global assessment of change in crow's feet lines, facial lines outcomes questionnaires, self-perception of age, and subject satisfaction of appearance have predominantly been applied [7, 8]. All of these evaluations use a subjective scaling of facial lines (observer-reported outcomes) or a validation of the patients' (subjective) perceptions (patient-reported outcomes) for wrinkles and overall age appearance. However, subjective assessments alone are prone to error and can be challenging for different skin types [9]. BoNTA has been used for decades, and in this context, it is adequate to apply an objective assessment for validation of its effects and duration [10].

Following the establishment of an objective methodology [11] the aim of this prospective work was to analyze the three-dimensional documentation (objective evaluation) of BoNTA treatments on the static (wrinkle depth) and dynamic (muscular activation) effects of glabellar lines after 30 and 90 days, and to evaluate patient-reported as well as physician-reported results.

Materials and Methods

Study Design and Patients

The protocol was approved by the Institutional Review Board (29-521) of the Medical University of Graz, Austria. We evaluated prospectively collected three-dimensional photographs of 21 female outpatients aged 21–64 years from 12/2013 to 04/2014. Inclusion criteria for this retrospective analysis were mild-to-moderate glabellar lines assessed using the glabellar line scale from Merz Aesthetics Scales [12] at rest (values 1 and 3) and mild-to-severe dynamic glabellar lines (values 1–4), where all participants confirmed no treatment, e.g., with botulinum toxin and/or facial fillers, in the upper face up to 1 year before enrollment. An additional participation requirement was the omission of any additional aesthetic treatments in the upper facial region during the observed period. Participants received a total of 20 units [13] of BoNTA (Xeomin, Merz, Frankfurt am Main, Germany), with two injection sites per corrugator supercillii muscle (10 units per muscle): 5 units in the muscle belly and 5 units in the lateral skin insertion (Fig. 1). Following informed consent (photograph documentation, treatment), we performed the three-dimensional assessment [11] and glabellar line scale [12] before treatment (pretreatment), and on day 30 and 90 of follow-up (day 30 and 90 posttreatment) (Table 1). As

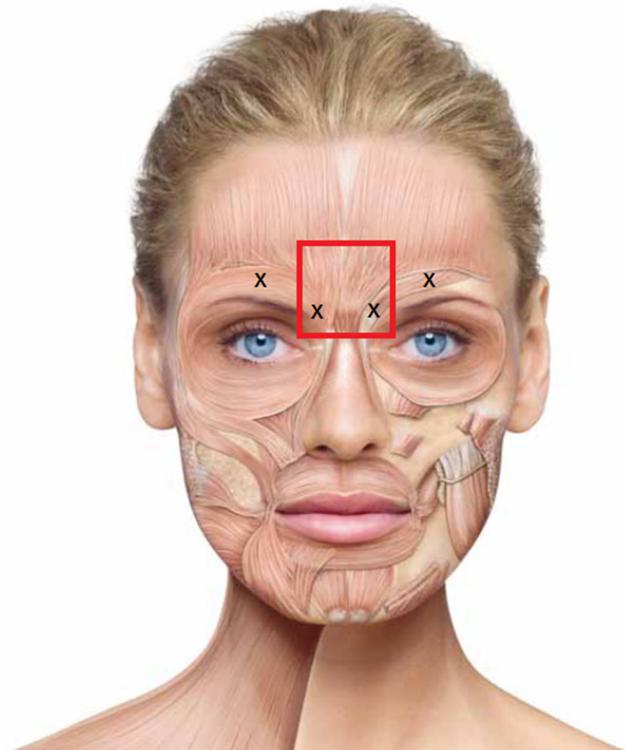


Fig. 1 Injection sites on the corrugator supercillii muscles are marked with black crosses; the field of view containing the region of interest is highlighted in red (the picture has been provided by Merz Pharmaceuticals GmbH, Germany)

standard procedure at our institution patients were asked to wait for 30 min following treatment to observe for bruising and adverse events before leaving the private practice. In case of bruising, cool packs were immediately applied.

Digital Photograph Documentation

At our institution we were using the 3D LifeViz Micro system (Quantificare S.A., Sophia Antipolis, France) to record the glabellar area (highlighted in red, Fig. 1) before (pretreatment) as well as 30 and 90 days (posttreatment) after treatment with BoNTA. The integrated light sensor allowed for standardization of the distance between skin and lens at 20 cm. In addition, the focus point was marked between the two eyebrows (Fig. 1) to create a reproducible reference per visit for each patient. We took two pictures per patient and session: neutral facial expression (position 1 as seen in Fig. 2) and firmest possible bilateral eye closure (position 2 as seen in Fig. 3) as previously published [11]. Private practice appointments for all study participants were on standardized time intervals (weekdays, between 4 pm and 8 pm), and stereophotography was performed under standardized lighting conditions in the same office.

Table 1 Timetable of evaluated parameters

	Pretreatment	Day 30 posttreatment	Day 90 posttreatment
Clinical assessment	X [#]	X	X
Objective 3D photography	X	X	X
Subjective glabellar line scale	X	X	X
Overall patient satisfaction			X

[#]Assessments were performed before BoNTA injections and 30 min thereafter



Fig. 2 Position 1 with neutral facial expression demonstrates static changes of glabellar wrinkles: left: pretreatment, center: day 30 posttreatment, and right: day 90 posttreatment



Fig. 3 Position 2 with firmest possible bilateral eye closure demonstrates dynamic changes of glabellar frown lines: left: pretreatment, center: day 30 posttreatment, and right: day 90 posttreatment

The surface irregularity was calculated by a blinded assessor using the DermaPix software (Quantificare S.A., Sophia Antipolis, France) as previously published (Fig. 4) [11].

Primary and Secondary Endpoints

The primary endpoint was the timely change of surface irregularity as assessed by objective stereophotography in the glabellar region: Static changes (“wrinkle depth” in the glabellar region) were defined as the timely evolution of surface irregularity in position 1. Dynamic changes (muscular activation) were defined as timely development of surface irregularity in position 2 to record the active ability of the firmest possible bilateral eye closure to mimic a maximal frown in the glabellar region.

Secondary endpoints included the subjective glabellar line scale, from the Merz Aesthetics Scales [12], which was used to subjectively grade the glabellar lines by matching the patient’s wrinkles to the supplied standardized photographs of the 5-point rating scale at rest (“static”: 0 = no glabellar lines, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe glabellar lines) and during firmest possible bilateral eye closure (“dynamic”: 0 = no glabellar lines, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe glabellar lines) by the treating physician. In addition, complications (which included: bluish effusion, swelling at injection site, or other adverse reactions e.g., eyelid ptosis), and overall patient satisfaction was assessed by two questions on day 90 posttreatment (1. Did you observe a wrinkle improvement in the glabellar region: yes or no?/2. Would you repeat this treatment: yes or no?) (Table 1).

This study was conducted in a private practice setting for quality assessment purposes, and each subject signed an informed consent form, that the obtained three-dimensional documentation and related use for scientific purposes could have been performed. The prospectively conducted data collection was performed according to the Declaration of Helsinki to preserve patients’ rights, and the three-dimensional documentation required no additional approval of the local institutional review board.

Data Analysis

Collected images were labeled using DermaPix software and the region of interest for software-based calculation (Fig. 4), manually marked in the field of view (red area, Fig. 1) by a blinded assessor. Results were exported into an Excel spreadsheet (Microsoft, Richmond, VA, USA) and appropriately sorted.

For descriptive statistics, parametric data were presented in mean \pm standard deviation, nonparametric data in median (min–max), if not otherwise stated. Percent changes were calculated using the mean value from pretreatment assessed by stereophotography divided by the mean values achieved on day 30 and day 90 posttreatment expressed in percent. Following assessment of (non)parametric distribution by the Shapiro–Wilk normality test, we evaluated parametric data with the one-way analysis of

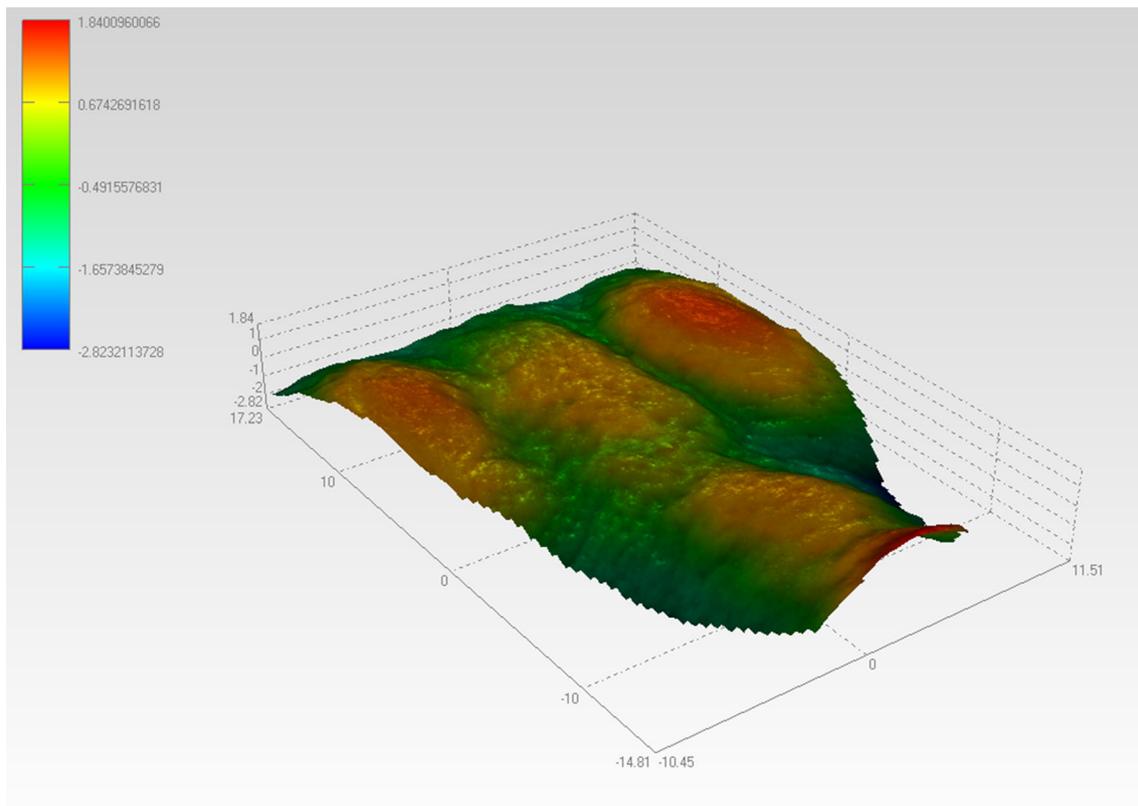


Fig. 4 Three-dimensional reconstruction of the region of interest using DermaPix software

variance (ANOVA) followed by Tukey's multiple comparison test (surface irregularity static frown lines and firmest possible bilateral eye closure, glabellar line scale). A p value of < 0.05 was considered statistically significant. Data were analyzed using GraphPad (Prism 5 software, La Jolla, CA, USA).

Results

All 21 patients completed the 90-day follow-up, and there were no additional treatments in the stated facial region performed in any of the participants during this period.

Static Assessment

The surface irregularity of static glabellar lines (neutral facial expression) as assessed by the objective three-dimensional setup was significantly reduced by -17% and -24% on day 30 and 90 posttreatment, respectively (posttreatment vs. pretreatment; both $p < 0.0001$; Table 2 and Fig. 5).

We found no statistically significant differences in the subjective static glabellar line scale (Table 3) comparing

Table 2 Overview of the change of surface irregularity for each position and time point

	Pretreatment	Day 30 posttreatment	Day 90 posttreatment
<i>Neutral position</i>			
Mean	0.0091	0.0076	0.0069
% Change	n/a	-17%	-24%
SD	0.0029	0.0023	0.0020
p value		< 0.0001	< 0.0001
<i>Firm eye closure</i>			
Mean	0.0121	0.0090	0.0095
% Change	n/a	-26%	-21%
SD	0.0034	0.0030	0.0026
p value		< 0.0001	< 0.0001

Mean values are presented in mm; % change and p -values are calculated in comparison with pretreatment, SD standard deviation

pretreatment (1.9 ± 0.7), day 30 posttreatment (1.3 ± 0.8), and day 90 posttreatment (1.3 ± 0.8).

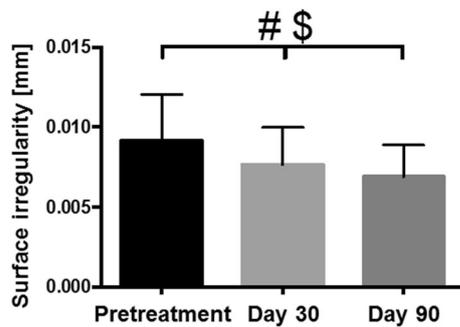


Fig. 5 Objective stereophotographic changes of static glabellar wrinkles over time (position 1, neutral facial expression). Statistically significant differences of the surface irregularity in the glabellar region were seen comparing pretreatment versus day 30, day 30 versus day 90, and pretreatment versus day 90 posttreatment (# one-way ANOVA: $p < 0.0001$; \$ Tukey's multiple comparison test: $p < 0.05$). Columns represent mean values, and error bars the standard error of mean

Table 3 Overview of the change of surface irregularity for each position and time point

	Pretreatment	Day 30 posttreatment	Day 90 posttreatment
<i>Neutral position</i>			
Mean	1.9	1.3	1.3
% Change	n/a	− 32%	− 32%
SD	0.7	0.8	0.8
<i>p</i> value		ns	ns
<i>Firm eye closure</i>			
Mean	2.8	1.5	2.5
% Change	n/a	− 46%	− 11%
SD	1.0	0.8	1.0
<i>p</i> value		< 0.05	ns

Means are values from Merz Aesthetics Scales; % change and *p*-values are calculated in comparison with pretreatment, *SD* standard deviation, *ns* not significant

Dynamic Measurements

Using the objective three-dimensional assessment, dynamic glabellar frown lines (position 2: firmest possible bilateral eye closure) demonstrated a reduction of surface irregularity by − 26% and − 21% on day 30 and 90 posttreatment, respectively (vs. pretreatment; both $p < 0.0001$; Table 2 and Fig. 6). No significant changes were observed on day 30 versus day 90 posttreatment. The highest percentage in the reduction of surface irregularity was observed on day 30 posttreatment versus pretreatment (− 26% for firm eye closure).

The subjective dynamic glabellar line scale (Table 3) confirmed a statistically significant improvement for day

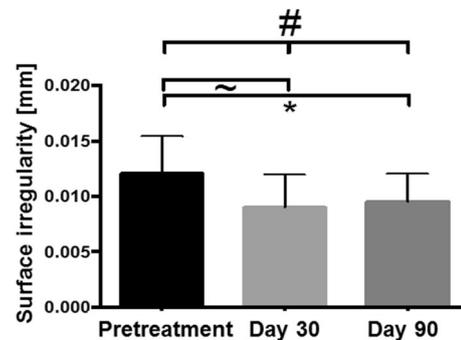


Fig. 6 Objective stereophotographic changes of dynamic glabellar frown lines over time (position 2, firmest possible bilateral eye closure). Statistically significant differences of the surface irregularity in the glabellar region were seen comparing pretreatment versus day 30 posttreatment, and pretreatment versus day 90 posttreatment (# one-way ANOVA: $p < 0.0001$; Tukey's multiple comparison test: ~ pretreatment versus day 30, *pretreatment versus day 90, $p < 0.05$). Columns represent mean values, and error bars the standard error of mean

30 posttreatment (1.5 ± 0.8) versus pretreatment (2.8 ± 1.0 ; $p < 0.05$), and a statistically significant scale return to pretreatment values from day 30 posttreatment (1.5 ± 0.8) to day 90 posttreatment (2.8 ± 1.0 ; $p < 0.05$). There were no statistically significant differences in dynamic glabellar line scales between pretreatment (2.8 ± 1.0) and day 90 posttreatment (2.5 ± 1.0).

Complications and Patient Satisfaction

Two patients presented with small bruising at the injection site immediately after injections, with no further complications observed throughout the 90-day period in any of the other participants.

On day 90 posttreatment, all 21 analyzed participants stated that their glabellar lines had improved and that they would repeat the treatment.

Discussion

We demonstrated an ongoing effect of BoNTA treatment on glabellar frown lines by subjective patient- and physician-reported outcomes over 3 months and confirmed the results by objective three-dimensional assessment of static (position 1: “less wrinkling, smoother surface”; Fig. 2) and dynamic changes (position 2: lack of muscle-activated twitching; Fig. 3), both measured as surface irregularity over time. The established three-dimensional setup [11] proved to be a reliable asset in the quantification of BoNTA treatment in clinical practice for quality assessment purposes. Since wrinkles were calculated as surface irregularity (volume divided by surface area), the setup can be

simplified for scientific evaluation of (static) volume changes induced by facial fillers omitting the requirement to analyze dynamic changes.

BoNTA treatment resulted in a long-lasting and increasing reduction of skin irregularity, reflected as an objective static reduction of glabellar wrinkles with a significant impact on day 30 and day 90 with -17 and -24% (vs. pretreatment), respectively. Wrinkles, in this case expressed as objective static surface irregularities on neutral facial expression (position 1, Fig. 2), can be a marker for aging (also for hyperactive facial muscle activity), if observed intra-individually over time [14]. The predominant aesthetic purpose for using different types of neurotoxins (“botox”) is the reduction of effects related to facial aging [15]. A youthful look is a pivotal factor in a given human’s physical appearance and contributes tremendously to the self-perception of each individual [16]. It is this very subjective feature of self-perception, also reflecting an individual’s physiological and psychological balance, which renders all subjective (self-)assessment scales biased. In this context, the herein presented setup is suitable for filling the gap of a so far lacking clinically applicable objective support [10] for scientific analysis of aesthetic treatments of facial wrinkles, where subjective assessments as primary study endpoints prevail [7, 8, 17].

The reduction of the ability for facial expressions is also a result of the injected toxins. We quantified the loss of muscle function in the glabellar region by assessing dynamic changes resulting from firm eye closure (= production of maximum glabellar frown) (position 2, Fig. 3), where a maximum effect was observed after 30 days (-26% reduction), and still effective on day 90 post-treatment (-21% reduction, both vs. pretreatment). This objective finding in our study was also confirmed by Caruthers in a subjective fashion: A significant improvement in satisfaction with appearance and self-perception was most prominent on day 30 after treatment [17]. The main advantage of the presented approach is its noninvasiveness, swift documentation and proven applicability for documentation in a private practice setting. In comparison with previous trials of objective wrinkle assessment no cumbersome analysis using cast prints [5] or electrode measurements as required for obtaining adequate electromyography results [6] were required.

A recent review on the safe dosage of BoNTA for the treatment of glabellar lines showed that the most common endpoint of all double-blind randomized controlled trials to assess the effects of BoNTA was the Facial Wrinkle Scale [18]. However, only a few validated facial grading scales have so far become available [19]. Most of these subjective scales evaluated the key signs of the aging upper face and demonstrated excellent reproducibility and reliability [9]. In our opinion, also as a result of the subjective feature of

aesthetic treatments, the continuous assessment of the subjective outcomes either by patients or by treating physicians themselves is undoubtedly an integral part of a therapeutic evaluation of BoNTA treatments. We have included the glabellar line scale for subjective assessment concomitantly on all study time points [12] and found that subjectively assessed facial features were “missed by the human eye”: Only dynamic changes were (significantly) caught by the non-blinded rater on day 30 (vs. pretreatment). The dynamic changes on day 90 were rated just like the pretreatment values, and static changes were missed altogether. This is in contrast to the three-dimensional technique, which revealed a (statistically significant) continuous improvement of static facial wrinkles, despite the (statistically not significant) reduction of dynamic glabellar frowning from day 30 to day 90 posttreatment. The objective three-dimensional approach was therefore able to detect even minor changes in facial surface irregularity by using high-resolution imaging and computerized software analysis.

The limitations of our study include the evaluation of the glabellar line scale by a non-blinded rater, the requirement for a manual computerized workup of the three-dimensional documentation (lack of automation), and the follow-up period of 90 days. Most participants presented for BoNTA, but also additional treatments. Upon recruitment, we defined a follow-up period of 90 days with no additional aesthetic interventions as a participation requirement, which might have affected the documentation results. Appropriate facial rejuvenation approaches include all available techniques, also dermal fillers, and form part of a minimally invasive cosmetic workup, which was only begun after the documentation period [4].

Three-dimensional assessment tools have become an important source of innovation to simulate and predict technological interventions on the breast(s) [20], nose [21], and other parts of the body [22]. Patients appreciate clearly defined outcomes to ensure fulfillment of their wishes and expectations by the relevant aesthetic procedure. A three-dimensional assessment is an excellent tool for filling the (objective) gap in the scientific evaluation of injectable solutions in clinical trials. In this context, the presented noninvasive three-dimensional documentation proved to be a focused objective tool, which can provide an objective efficacy determination of injectable solutions for scientific and clinical trial purposes.

Authors’ contributions All authors made substantial contributions to the conception and design (DBL, TR, PW), data acquisition (DP, PW), analysis (DBL, ACT, PW), interpretation (ACT, DBL, SM, TR, PW, LPK), drafting of the manuscript and its revision for important intellectual content (all authors).

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Compliance with ethical standards

Conflict of interest Dr. Thomas Rappl is a consultant and investigator to Merz Pharmaceuticals GmbH, Germany. All the other authors have no conflict of interest to declare.

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