Preliminary Report on an Objective, Fast, and Reproducible Method to Measure the Effectiveness of Botulinum Toxin Type A

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Abstract

Background: The injection of botulinum toxin type A for cosmetic proposes is a popular procedure, although the interpretation of its effectiveness still poses a challenge. In fact, although the methods that evaluate the efficacy of the treatment are validated and reliable, they are usually based on subjective scales, while an objective and quantitative scale is still needed.

Objectives: I propose an objective, fast, and reproducible method to evaluate the severity of wrinkles with a three-dimensional imaging and texture analysis.

Methods: Digital Analysis of the Cutaneous Surface (DACS) is employed to analyze cutaneous texture. Measures are performed in the glabellar area before and one month after infiltration of 15 units of onabotulinumtoxin-A.

Results: Eight women were included in this study. DACS was able to detect improvements in all cases. On average, static lines decreased by 12.4% and dynamic lines by 41.2%.

Conclusions: DACS provides an objective, direct, fast, and reproducible method to measure the results of botulinum toxin type A usage. It avoids the use of subjective scores, gives a direct measure of the wrinkles, is simple to perform, and allows the operator to analyze only the desired area.

Level of Evidence: 4

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Botulinum neurotoxin type A (BoNT-A) inhibits neural conduction by interfering with the release of acetylcholine. After binding selectively to presynaptic receptors, it is internalized. When intracellular, the toxin cleaves a membrane protein that allows acetylcholine exocytosis. The use of BoNT-A for aesthetic purposes was introduced by Carruthers in 1992 for glabellar frown lines. This application focused increased attention on this toxin until the United States Food and Drug Administration approved it in 2002 for glabellar wrinkles. The injection of type A botulinum toxin for cosmetic applications became a popular procedure, and different BoNT-A formulations were subsequently introduced over time, bringing about substantial changes in the field of aesthetic medicine. According to the American Society for Aesthetic Plastic Surgery, 3,766,148 cosmetic procedures with BoNT-A were performed in 2013, showing a growth of 15.6% over 2012.

In spite of the widespread use of this procedure and the multiplicity of studies on this topic, the interpretation of effectiveness still presents a challenge.

Several methods of measurement have been described. They rely on subjective evaluations and only a minority of these are considered reliable and reproducible. These measurements employ an arbitrary scale or they measure improvement or worsening from baseline. Heckmann evaluated the effectiveness of a digital method to measure the effects of BoNT-A on frontal wrinkles.

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An objective and quantitative scale is still needed for the evaluation of severity of rhytides and for monitoring of the effectiveness of cosmetic BoNT-A treatment. I propose an objective, instrumental, and reproducible method to evaluate the severity of wrinkles with a three-dimensional imaging and texture analysis of the epidermis.

**MATERIALS AND METHODS**

**Measurement**

The patients included in this study were evaluated by Digital Analysis of the Cutaneous Surface (DACS). DACS consists of the digital acquisition of multi-spectral photographs of a determined area, measuring the exact melanin content, hemoglobin concentration, wrinkles, and texture. In this study I analyzed only wrinkles and texture, discarding the information concerning melanin content and hemoglobin concentration. The measures were made with the Antera device (Antera 3, Miravex Limited, Dublin, Ireland).

The method relies on multi-directional illumination and computer-aided reconstruction of the skin surface, illuminating the surface from different angles and using the differences between these images to reconstruct the surface in three dimensions. The skin topography and the chromophore concentration are derived from the spatial and spectral analysis of the acquired image data, obtained by illuminating the skin with light-emitting diodes of different wavelengths shining from different directions (Figure 1).

The reconstruction of the skin texture is achieved using a technique based on shape from shading, extensively modified in order to eliminate skin glare and improve the accuracy of measured data. The texture reconstructed in this way is then used for quantitative skin analysis, such as depth and width of wrinkles, lesions of the skin, and overall skin roughness.

Wrinkles are assessed as follows:

1. **Overall skin curvature suppression.** In this step the skin is “straightened” using specific “wrinkle filter settings,” which take into account the natural curvature of the skin. The filter tells the program that surface features of lateral size higher than the filter value are to be considered as the natural curvature of the skin and suppressed.

2. **Along the selected strip, the deepest point is calculated for each position.** Because this depth varies along the wrinkle, the average value from all depths is also calculated.

3. **The width of the wrinkle is calculated along its length.** The boundary points of the wrinkle are defined as those that do not exceed approximately 1/10 of the maximum depth. From this set of widths, the average value is calculated.

4. **The overall size is proportional to the cross-section within the wrinkle boundary.** The boundary level is taken as a reference (zero depth).

Skin roughness is calculated (after overall skin curvature suppression) as “roughness average,” with roughness plane modification, applying the following algorithm:

$$Ra = \frac{1}{n} \sum_{i=1}^{n} |y_i|$$

After acquisition of images, the operator can select the desired area. In my study I marked the glabellar region with five marker points.

Texture is evaluated in this area after three-dimensional reconstruction (Figure 1).

Each measure was performed in the resting and in the hyperkinetic state. The variation of skin wrinkles is expressed by means of a percentage between the two measured values (Figure 2).

**Patients**

Eight patients recruited for treatment with onabotulinumtoxin-A from September 2012 to January 2013 were included in the study. Treatment with BoNT-A for glabellar rhytides does not require the Institutional Review Board approval in Italy.

Informed consent was obtained in all cases. Exclusion criteria were: previous treatments with resorbable fillers in the previous 12 months, previous treatment with non-resorbable fillers, anticoagulant consumption, previous nasal surgeries or face lifts, and treatment with BoNT-A in the previous 6 months.

Patients were affected by mild to moderate rhytides in all cases and underwent infiltration of 15 units of BoNT-A in five points, targeting the procerus, depressor superciliii,
and corrugator supercilii muscles. Each patient was studied with DACS before the procedure and between two and four weeks after the procedure. Both resting and dynamic measures were performed. The variation in skin wrinkles was recorded.

**RESULTS**

Eight women, aged from 36 to 66 years (50-year-old mean) and affected by glabellar wrinkles, were enrolled in the study.

Skin wrinkles decreased in all cases, with mean improvement of 12.4% for resting and 41.2% for hyperkinetic lines. The static improvement ranged between 11.6% and 54.2%, while the dynamic improvement ranged between 26% and 77.5%.

Three-dimensional images display the improvements induced by BoNT-A concerning texture and wrinkles (Figures 3-6).

**DISCUSSION**

The objective evaluation of the effect of BoNT-A remains an open issue in the field of aesthetic medicine.

Several methods have been described to measure the effectiveness of BoNT-A, based on subjective scales. Carruthers proposed a photonumeric scale for forehead wrinkles with a score from 1 to 5, under static and dynamic conditions, known as the Forehead Lines Grading Scale. The same author described a similar scale for crow’s feet wrinkles.

Alam proposes a quality scale that includes the evaluation of several parameters: costs, risks, procedure time, discomfort, results, and longevity of results, although the evaluation of the results and longevity is subjective.

The “Home of Younger Skin” program enables one to perform a comprehensive evaluation of skin age. This software evaluates 35 subregions of the face, comparing the patient to a typical photograph of a sample patient at age 25, 35, 45, 55, or 65 years and attributing five grades of aging of the considered feature in a Likert scale. This software relies on control photographs and does not quantify the skin wrinkles of the skin.

Heckmann proposed an interesting scale to measure the effects of BoNT-A on frontal wrinkles with a digital method. In this study the authors employ digital photographs to measure the mobility of brows and the brow-to-brow distance. This method consists in an objective measurement of the effect of the cosmetic effect of BoNT-A, although it relies on an indirect measurement of the wrinkles by measuring brow parameters.

In my study, I employed the Digital Analysis of the Cutaneous Surface (DACS) and evaluated the effects of BoNT-A. This method analyzes the cutaneous texture with...
a tridimensional reconstruction of the skin surface. The operator is able to delimit an area to analyze, which the software recognizes during the subsequent acquisition on the same patient. An algorithm then analyzes the skin wrinkles of the skin, calculating the percentage of variation from the first measurement.

This measurement has not been matched to other scales. The comparison requires bigger samples, but this is not the aim of this preliminary report. The comparison of DACS and the Facial Wrinkle Scale is in progress.

The limitations of the study are the small sample size, which does not allow this method to be validated for a
standardized measure of BoNT-A effects, and the absence of a control group. Patient satisfaction was not measured.

A total of 15 units of BoNT-A were used in all cases, with rhytides from mild to moderate. This posology is below the Food and Drug Administration–indicated dosage of 20 units, the standard for the glabella in the United States. The lower posology was preferred to fit the different muscular patterns and rhytides and to meet the desire of those patients who asked not to achieve a “frozen” effect.

In my opinion, DACS offers a numerical and mathematical, objective, direct, fast, and reproducible method. In fact, this method avoids the use of subjective scores. Moreover, the measurement of the wrinkle is direct,
avoiding indirect parameters of wrinkles (eg, brow-to-brow distance). The software instead considers length, width, and depth of each line, wrinkle, or fold.

The evaluation of rhytides with DACS has several differences, with evaluations based on subjective scales.

- The area to be treated and evaluated can be customized and selected by the operator. This is very useful for making a selective evaluation of the effectiveness of BoNT-A in different regions.
- The “roughness” of the skin is calculated with an algorithm and can be applied virtually in every region.
- The results are objective and not subjective. Moreover, the measurement is reproducible and exact because the area to be evaluated is digitally recognized and measured.
- Both static and dynamic rhytides can be measured.
- The skin roughness is a continuous ordinal variable and not an interval-scale variable. This allows a more accurate analysis of the achieved results.

In this preliminary report I observed a decrease in skin wrinkles in all cases. Only limited improvement was seen in skin texture (static wrinkles). This could be explained by several factors:

- The considered sample is limited and includes only patients without mild-to-moderate wrinkles. Greater improvements would have been expected in patients with severe wrinkles.
- Skin texture in the measured area is the product of the action of several muscles, and BoNT-A was not injected in all of these.
- The cutaneous lines resulting from wrinkles could not be completely removed, even after complete paralysis of the muscles.

CONCLUSION

The evaluation of the efficacy of BoNT-A is still an open topic. It is usually expressed with scores that consider subjective evaluations and photonumeric scales. I propose the use of a Digital Analysis of the Cutaneous Surface (DACS). This method employs a three-dimensional reconstruction and expresses a quantitative measure of skin wrinkles, evaluating length, width, and depth of each line, wrinkle, or fold. An algorithm recognizes the same area during the subsequent acquisitions. This method differs from other validated methods used to evaluate lines. In fact, this procedure does not rely on photonumeric scales but uses a direct, precise, and quantitative measure of the lines. The procedure is fast, inexpensive, and reproducible.

I believe that DACS provides for an objective, direct, fast, and reproducible method that could be currently applied for monitoring the effectiveness of any cosmetic procedure with BoNT-A.

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REFERENCES