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Facing depression with botulinum toxin: A randomized controlled trial

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ABSTRACT

Positive effects on mood have been observed in subjects who underwent treatment of glabellar frown lines with botulinum toxin and, in an open case series, depression remitted or improved after such treatment. Using a randomized double-blind placebo-controlled trial design we assessed botulinum toxin injection to the glabellar region as an adjunctive treatment of major depression.

Thirty patients were randomly assigned to a verum (onabotulinumtoxinA, $n = 15$) or placebo (saline, $n = 15$) group. The primary end point was change in the 17-item version of the Hamilton Depression Rating Scale six weeks after treatment compared to baseline.

The verum and the placebo groups did not differ significantly in any of the collected baseline characteristics. Throughout the sixteen-week follow-up period there was a significant improvement in depressive symptoms in the verum group compared to the placebo group as measured by the Hamilton Depression Rating Scale ($F_{(6,168)} = 5.76$, $p < 0.001$, $\eta^2 = 0.17$). Six weeks after a single treatment scores of onabotulinumtoxinA recipients were reduced on average by 47.1% and by 9.2% in placebo-treated participants ($F_{(1,28)} = 12.30$, $p = 0.002$, $\eta^2 = 0.31$, $d = 1.28$). The effect size was even larger at the end of the study ($d = 1.80$). Treatment-dependent clinical improvement was also reflected in the Beck Depression Inventory, and in the Clinical Global Impressions Scale.

This study shows that a single treatment of the glabellar region with botulinum toxin may shortly accomplish a strong and sustained alleviation of depression in patients, who did not improve sufficiently on previous medication. It supports the concept, that the facial musculature not only expresses, but also regulates mood states.

1. Introduction

Affecting 121 million people, depression is one of the leading causes of disability in the world (WHO, http://www.who.int/mental_health/management/depression/definition/en/). Although there are various effective treatments, therapy response is unsatisfactory and depression becomes a chronic condition in a considerable proportion of patients (Gilmer et al., 2005). Thus, there is a need to develop further therapeutic techniques to improve the course and the prognosis of depressive disorders.

Negative emotions, like anger, fear, and sadness, that are prevalent in depression are associated with activation of the corrugator and procerus muscles in the glabellar region of the face (Ekman and Friesen, 1978). Accordingly, in patients with depressive disorders facial electromyography reveals a relative overactivity of the corrugator muscles during different affective imagery paradigms (Schwartz et al., 1976). Activation of the corrugator muscles is also correlated with psychomotor agitation in depression and contributes to facial features like the 'omega melancholicum' and Veraguth's folds (Greden et al., 1985). Charles Darwin (1872)

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perceived these features as a very specific expression of sadness and attributed them to the activity of so-called 'grief muscles' in the glabellar region (Darwin, 1872).

"Refuse to express a passion, and it dies", this aphorism by William James (1890) refers to the facial feedback hypothesis, which implies mutual interaction between emotions and facial muscle activity (Darwin, 1872; James, 1890). In fact there is experimental evidence that voluntary contraction of facial muscles can channel emotions, which are conversely expressed by activation of these muscles (Strack et al., 1988; Larsen et al., 1992).

Injection of botulinum toxin to the glabellar region inhibits the activity of the corrugator and procerus muscles. This effect is used in the cosmetic treatment of frown lines (Carruthers and Carruthers, 1992). Facial treatment with botulinum toxin has become the most frequent intervention in esthetic medicine with estimated applications of several million per year (American Society of Plastic Surgeons Report of the 2010 Plastic Surgery Statistics, http://www.plasticsurgery.org/Documents/news-resources/statistics/2010-statisticss/Top-Level/2010-US-cosmetic-reconstructive-plastic-surgery-minimally-invasive-statistics2.pdf).

Treatment of the glabellar region with botulinum toxin produces a relative change in facial expression from angry, sad, and fearful to happy and can impact on emotional experience (Heckmann et al., 2003; Davis et al., 2010). Recipients of this treatment reported an increase in emotional wellbeing beyond the cosmetic benefit (Sommer et al., 2003). Specifically, reduced levels of fear and sadness were observed (Lewis and Bowler, 2009). The treatment also attenuated the activation of limbic brain regions during voluntary contraction of the corrugator and procerus muscles, indicating that feedback from the facial musculature may modulate the processing of emotions (Hennenlotter et al., 2009). Hence, the processing time for sentences with negative affective connotation was prolonged in women after glabellar botulinum toxin treatment and the treatment interfered with the ability to decode the facial expression of other people (Havas et al., 2010; Neal and Chartrand, 2011). The capacity of this intervention to counteract negative emotions may also be of clinical use. Accordingly, preliminary data from an open case series with ten female patients indicate that it may reduce the symptoms of depression (Finzi and Wasserman, 2006). We hypothesized that facial psychomotor features associated with depression are not just epiphenomena but integral components of the disorder and may be targeted in its therapy. To explore, if attenuation of these features may produce alleviation in the affective symptoms, we conducted a randomized controlled trial of botulinum toxin injection to the glabellar region as an adjunctive treatment of major depression.

2. Materials and methods

2.1. Trial design

At two centers, the Psychiatric University Hospital of the University of Basel, Switzerland and the Medical School Hannover, Germany we conducted a randomized, placebo-controlled, double-blind trial from August 2009 through October 2010. The trial has been registered with ClinicalTrials.gov, number, NCT00934687. The study was investigator-initiated and was carried out independently of any commercial entity. It was funded solely by the Gottfried & Julia Bangerter-Rhyner-Stiftung, Bern, Switzerland, a private foundation that supports medical research (http://www.bangerter-stiftung.ch/). The study protocol was approved by the institutional review boards, the local ethic committees and the Swiss and German regulatory authorities. It comprised seven visits (baseline, two weeks, four weeks, six weeks, eight weeks, twelve weeks, and sixteen weeks after baseline).

A power analysis based on the observations from the open case series (Finzi and Wasserman, 2006), allowing for an equal placebo control group with a theoretical 50% improvement, indicated that a sample size of <30 participants would be sufficient to detect comparable effects with a power of $>80\%$ at a significance level of $p < 0.05$.

2.2. Participants

Participants were recruited from local psychiatric outpatient units, psychiatrists in private practice, or through advertisements placed in the local press. The method under investigation, i.e. botulinum toxin treatment, was not explicitly mentioned in the advertisement, in order to avoid attracting candidates who were primarily motivated by receiving this treatment for cosmetic reasons. Both men and women were included. Inclusion criteria were: age 25–65 years, on-going major depressive disorder (DSM-IV 296.xx) diagnosed according to the Structured Clinical Interview for Axis I DSM-IV disorders (SCID I; $\geq$15 points on the Hamilton Depression Rating Scale at screening) with or without a history of dysthymic disorder (DSM-IV 300.4), and a moderate to severe vertical glabellar line during maximum voluntary frowning according to a four-point clinical severity score (Honeck et al., 2003) as well as qualitatively and quantitatively stable treatment with one or, at most, two antidepressants for at least four weeks. For ethical reasons we did not include untreated patients unless they had not responded to at least one treatment trial with an antidepressant during on-going index episode and were reluctant to undergo another one.

Exclusion criteria were: psychotic symptoms, suicidal tendency, clinical severity requiring immediate intervention, further DSM-IV axis I diagnoses, clinically manifest personality disorder, severe premenstrual syndrome or premenstrual dysphoric syndrome, regular occurrence of migraine or other forms of cephalalgia, psychological strain associated with glabellar frown lines, contra-indications of botulinum toxin treatment, previous treatment with botulinum toxin, further psychopharmacological treatment other than a demand medication with limited amounts of sedatives or hypnotics (lorazepam up to 4 mg/week, oxazepam, up to 60 mg/week, zolpidem up to 20 mg/week, or zopiclone up to 15 mg/week), and on-going disorder-specific psychotherapy or any other specific therapy of depression.

From all participants we collected psychopathological findings and a personal, medical, and psychiatric history. Response to antidepressant treatment during on-going index episode was assessed according to the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ; Fava and Davidson, 1996). Treatment resistance was rated on a graduated scale (Thase and Rush, 1997). Participants were subjected to a general physical and neurological examination. Complementary somatic diagnostic procedures were disposed if organic reasons for depression had not been sufficiently excluded previously. All patients provided written informed consent after complete description of the study and before inclusion. Participants promised to leave their antidepressant medication unchanged during the first six weeks of the trial. Thereafter, they were allowed to change their treatment in consultation with their physician.

2.3. Interventions

For the verum condition onabotulinumtoxinA (Vistabel®, Botox® Cosmetic, Allergan) was dissolved in 0.9% NaCl solution (B. Braun Medical) at a concentration of 100U/2.5 ml. Injections were