Mastication is a rhythmic activity that could be under the control of certain brainstem neurons. Probably corticobulbar neurons initiate mastication, but later feedback from peripheral sensory afferents of diverse mucous, joint and muscle receptors are likely required to modulate the activity of these brainstem neurons. Basal ganglia may play an important role in sensorimotor integration and modulation of brainstem and spinal cord interneurons excitability during mastication. Internal globus pallidus and sustantia nigra pars reticulata project to the brainstem nuclei by several pathways. Sustantia nigra reticulata innervates the parvicellular reticular formation, which has direct projections to the trigeminal and facial nerve muscles involved in mastication. Rhythmic firing has been demonstrated in interneurons of the pontine reticular formation that project to brainstem motor nucleus involved in mastication. Thus, we postulate that our patient could have abnormalities in sensorimotor integration and lack of control of rhythmic firing of brainstem interneurons due to the injured basal ganglia. The combination of these abnormalities could lead to the clinical expression of eating-induced facial myoclonic dystonia.

LEGEND TO THE VIDEO

Segment 1. The patient does not have facial dystonic activity while speaking but shows occasional myoclonic-like movements in her left perinasal and peribucal muscles at rest or during voluntary facial movements. Neither, is dystonia observed when she simulates mastication without food intake.

Segment 2. Every time she tries to chew solid food sustained contraction in her left perioral musculature appeared, causing dystonic deviation of the mouth and difficulties in chewing. Facial contraction finishes immediately when she stops chewing.

REFERENCES

The Effect of Injecting Botulinum Toxin Type A Into the Calf Muscles on Freezing of Gait in Parkinson’s Disease: A Double Blind Placebo-Controlled Pilot Study

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Abstract: Objective: To assess the effect on freezing of gait (FOG) of botulinum toxin type A (BTX-A) injections in advanced Parkinson’s disease (PD) patients. Method:

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BTX-A 150 IU or normal saline was injected into each leg’s calf muscles by a blinded investigator. FOG severity was assessed at set intervals (6-month follow-up). Results: Eleven age- and disease severity-matched PD patients with disabling FOG participated. Six patients received BTX-A and 5 received saline. No improvement was observed in either group over time. Leg weakness and falls lead to early termination. Conclusion: BTX-A injections to the legs did not improve FOG and might increase fall risk. © 2007 Movement Disorder Society

Key words: botulinum toxin; freezing of gait; Parkinson’s disease; falls

The pathophysiology of freezing of gait (FOG) as a unique disturbance of locomotion is poorly understood at the neural network and anatomical level.

Clinically, one can observe some similarities between FOG and dystonic gait. Both gait disorders can be influenced by behavioral modification, sensory, or motor tricks and are selectively experienced in specific “automatic” gait patterns. Recent studies showed that one of the causative factors of frozen gait is dis-synchronized contractions of leg muscles, including the gastrocnemius. On the basis of this data and the well-accepted role of botulinum toxin type A (BTX-A) for the treatment of dystonia, we speculated that, in addition to their local muscle relaxation effect, injected BTX-A could reorganize the pattern of muscular activity by acting through afferent pathways coming from the injected site—possibly originating in muscle spindles—and serve as a long-term ‘sensory trick.’

We had injected botulinum toxin type-A (BTX-A, Allergan, Irvine, CA) first to a single case4 and then in a nonblinded fashion5 into the calf muscles of 10 patients with Parkinson’s disease (PD) in whom FOG was the predominant and disabling symptom. Seven patients reported different degrees of improvement of FOG severity after treatment, with a clear temporal relationship between the injection and change in FOG: the improvement was noted at 6.3 weeks (range 2–12 weeks) and deteriorated afterwards. That pilot study was a cross-sectional one: we now assessed the effect of BTX-A on FOG using a prospective, double blind, placebo-controlled design.

METHODS

Eleven PD patients (3 females and 8 males) with FOG during the “OFF” state for at least 3 months were randomized to either BTX-A (Allergan, Irvine, CA) treated or saline-injected groups. All patients were diagnosed as having PD according to the accepted criteria6 by two independent movement disorders specialists. The patients had disabling FOG, having a score of at least 14 in the Freezing of Gait Questionnaire (FOG-Q),7,8 experiencing FOG episodes with duration of 3 seconds and more every day, which affect their walk and activity of daily living. However, only patients who were able to walk independently were included. None of the patients had ever been exposed to BTX-A. Baseline assessments were done 4 and 2 weeks before and on the day of injection. Another movement disorders specialist performed the injections in a double blind fashion. Randomization and substance preparation were done by the nurse who assigned serial numbers to the placebo- or BTX-A-containing vials, unaware of the injection protocol. BTX-A or normal saline 0.9% (placebo) were injected under electromyographic guidance into the gastrocnemius/soleus muscles of both legs, one injection (50 IU) in the lateral and medial heads of the gastrocnemius and one injection (50 IU) in the soleus muscles. BTX-A was injected at a total dose of 300 IU (150 IU per leg) diluted in NaCl 0.9% solution for a final concentration of 100 IU/2 mL (total of 6 mL). Saline (NaCl 0.9%) was injected in the same volume (total of 6 mL, 3 mL to each leg). Patients were assessed at weeks +2, +4, +8, +12, +16, and +20 postinjection, according to a standard protocol. Activities of daily living (ADL) and other parts of the Unified Parkinson’s disease rating scale (UPDRS)9 were assessed 4 weeks before injection, on the day of injection, and 4 and 20 weeks later. The UPDRS was measured while the patients were in the “ON” state. They also filled in FOG-Q at each visit. The subjective clinical global impression of change (SCGIC) from baseline in FOG severity was also used to evaluate the efficacy of treatment. Independent SCGIC ratings of patients and caregivers, side effects as assessed according to the falls question in the ADL part of the UPDRS, and leg muscle strength rated according to the Medical Research Council scale10 were recorded at each visit. The skin on patients’ legs was also inspected on every visit. Postinjection evaluations were performed by the same investigator that assessed the patients before injections and who was also blinded to the injected substance. Antiparkinsonian medications were kept stable throughout the study.

The study was approved by the Ethics Committee of Tel-Aviv Sourasky Medical Center and the Ministry of Health of the State of Israel, and all patients signed an informed consent form before screening for eligibility. The consent form contained detailed explanation of possible side effects, specifying also the possibility for transient legs weakness and the possibility of increase in falls frequency. Patients were asked to be alert and to keep detailed records of falls on a daily basis. The informed consent also stressed that in case of appearance of such
adverse effects, patients were instructed to contact the investigators and preventive measures had to be taken.

**Statistical Analysis**

We used mixed effects models for repeated measures to investigate changes over time in the subjects’ motor status to handle an unbalanced design where subjects have different numbers of repeated measures. A separate model was applied for each motor status parameter (the dependent variable) to assess the effect of time and group assignment were considered as the categorical fixed factors (independent variables).

The study was planned to be conducted on a total of 30, 40 patients, that would yield hypothetical power of 71, 80%, respectively (assuming FOG-Q as the main outcome). Unfortunately, because of side effects, only 11 patients were involved in the study, causing the observed power for $\alpha = 0.05$ and $n = 11$ to decrease to 29%.

**RESULTS**

There were 6 patients in the BTX-A group and the 5 in the saline group. Their mean age was 69.4 ± 10.2 years (range 56–86), they had experienced PD motor symptoms for 10.4 ± 4.6 years (range 3–18) and were similar in age, PD motor symptoms duration, the score on the motor part of the UPDRS and their Hoehn and Yahr stage (H&Y) at “ON.” The frequency of falls at baseline was higher in the placebo group.

Table 1 presents the results over the 20 weeks of follow-up in both groups. There was no significant time effect on either the ADL section (including the FOG item) or the motor part of the UPDRS. The saline group showed a significant improvement on the FOG-Q total score in the 16th week compared with baseline ($P < 0.05$), with mild deterioration towards week 20. There were no significant changes in the FOG-Q score over time in the BTX-A group. There was no clear tendency of improvement over time in any of the SCGIC scores.

**Side Effects**

Three of the 6 BTX-A patients and 2 of the 5 controls reported leg weakness, that could not be demonstrated on clinical assessment. Two BTX-A patients reported an increase of fall frequency after injection, with mild improvement 20 weeks after injection. Overall, the frequency of falls increased significantly in the BTX-A-treated group (Table 1). One control patient had mild weakness in the gastrocnemius muscles of both legs (Medical Research Council scale) accompanied by an increase in his falls frequency. The overall falls frequency in the saline group was not increased. The falls frequency at week 4 (maximal effect of BTX-A injections) was similar in both groups (Table 1). One patient from the BTX-A-treated group reported a decrease in the fall frequency after the injection, possibly because of an improvement in FOG, followed by deterioration towards the 20th week. One BTX-A patient and two control patients complained of leg muscle pain during the first 2 to 4 weeks after injections that disappeared afterwards. Skin changes on the legs in one BTX-A patient (diagnosed by a dermatologist as xerotic dermatitis) appeared 6 weeks after the injection and lasted until the end of the follow-up period: its association with the injections is unclear. An exacerbation of senile purpura appeared in the first week after injections in one BTX-A patient, and one control developed unilateral arthritis of the ankle joint 4 weeks after injection, which resolved spontaneously.

Interim assessment of the results after 11 patients while maintaining the blinding revealed increased falls and one patient broke his arm. On the basis of that observation the blinding was broken and analysis of the
results demonstrated increased falls among the BTX-A treated group. As a result, the study was terminated after enrolling only 11 patients.

**DISCUSSION**

The present pilot study failed to show any therapeutic benefit of BTX-A injections into PD patients' calf muscles on FOG. However, due to early termination because of increased fall risk among the BTX-A treated group, we were unable to draw any definite conclusions in regards to efficacy of BTX-A on FOG. There are several possible explanations for the increased falls risk among the BTX-A treated group. Given that the consent form contained detailed explanations of possible weakness and listed falls as a possible side effect, the power of suggestion could have played a role in their occurrence. In addition, our study population was based on patients with advanced PD and severe FOG. Such population is at high risk for falls in general and based on the small number of patients enrolled we call for word of cautious in regards to the association between BTX-A injections to the calf muscles and falls in PD. The present study could not repeat the results of our previously published open labeled study to suggest a strong placebo effect in the previous study.

The question where to inject BTX-A for FOG is open. We chose the calf muscles based on the data of Andrews who suggested that FOG episodes appear because of the activity of the gastrocnemius/soleus and hamstring muscles, with subsequent coactivation of the thigh flexors and extensors.

No satisfactory positive effect on FOG of the BTX-A injections to the calf muscles in Parkinsonian patients was confirmed in our study. Our results are similar to those reported in the paper by Wieler et al. who also failed to confirm an ameliorating effect of BTX-A injections into the gastrocnemius/soleus complex in 12 patients.

The small number of patients precludes making any firm conclusions. Another reason for uncertainty is a possible sampling bypass: patients that agreed to take part in this study suffered from prolonged PD with prominent motor symptoms and very disabling FOG that did not respond to any classical antiparkinsonian medications. The chances for such advanced patients to benefit from BTX-A are small and as discussed earlier, the risk for complications is high. The present study can, however, serve as a basis for power calculations for future controlled trials, which should take into an account the limitations of including patients with severe FOG and advanced disease.

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