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Lack of Effect of Botulinum Toxin on Cortical Excitability in Patients With Cranial Dystonia

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Abstract: The aim of this study was to verify whether botulinum toxin (BTX)-induced clinical improvement of cranial dystonia is associated with changes in the cortical silent period (SP), a measure of cortical excitability. By transcranial magnetic stimulation (TMS), high-intensity stimuli were delivered with a round coil centered at the vertex during a maximal muscle contraction of the orbicularis oculi. Motor evoked potentials (MEPs) and SPs were obtained from surface electrodes placed over the orbicularis oculi muscle before and 2 to 3 weeks after BTX-A injection into the affected muscles in 10 patients with cranial dystonia and 8 age-matched control subjects. BTX injection improved blepharospasm in all patients. Facial muscle SPs were significantly shorter in patients than in control subjects and did not significantly change after treatment, at the time of maximal clinical improvement. We conclude that the clinical improvement induced by BTX in patients with cranial dystonia is largely symptomatic. It does not appear to result from modulation of abnormal aspects of intracortical excitability, although these may play a role in craniofacial dystonia.

Key Words: botulinum toxin, silent period, TMS, blepharospasm

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The term cranial dystonia is currently used to describe a disorder that consists of dystonic spasms limited to or predominant in cranial musculature. The most common cause of cranial dystonia is Meige syndrome, which is characterized by the presence of spasms of the orbicularis oculi (blepharospasm) and involuntary movements of muscles supplying the mouth and jaw (oromandibular dystonia). The spasms may even extend extracranially to the cervical region or the limbs. Abnormalities in the central control of brainstem interneuronal excitability mediating the trigeminal reflex have been a well-documented neurophysiologic abnormality in patients with cranial and cervical dystonia.[1–3] In line with other forms of dystonias, the most likely pathophysiologic mechanism is an altered descending facilitative input from the cortex secondary to distorted basal ganglia control.[4] Functional magnetic resonance imaging studies, as well as intracortical excitability assessment with transcranial magnetic stimulation (TMS)[5] and regional cerebral blood flow measurements have all supplied evidence for a role of the primary motor cortex and sensorimotor areas in blepharospasm (BSP) and cranial dystonia.[6–8] Moreover, TMS and cortical silent period studies show evidence of increased excitability of the primary motor cortex in patients with BSP and cranial dystonia (CD).[9]

The use of botulinum toxin type A (BTX-A) has been a major therapeutic approach for the treatment of dystonia, spasticity, and other involuntary muscle contractions.[10] BTX-A acts at the neuromuscular junction, producing a transient chemical block of acetylcholine release from the presynaptic terminals. The induced muscle weakness might be entirely responsible for the transient amelioration of symptoms. However, an effect of BTX-A on central nervous system (CNS) structures cannot be entirely ruled out. Possible CNS effects of BTX include a direct effect on motoneurons after internalization and retrograde axonal transport.[11] There could also be an indirect effect on segmentary or long-loop reflex circuits triggered by neuromuscular junction blockade of γ-innervated muscle spindle fibers.[12,13] The toxin may also act directly on the CNS,[14] inhibiting the release of acetylcholine.[15]

The central effects of BTX are a matter of controversy: changes induced by BTX on reciprocal inhibition, at spinal levels, between agonist and antagonist muscles have been described in patients with dystonia[16] and suggest that BTX modifies spinal cord excitability. On the other hand, 2 studies of the blink reflex excitability recovery curve, using BTX injection in patients with cervical and cranial dystonia, did not show any changes in brainstem interneuronal excitability.[17,18] Patients with writer's cramp have been studied with TMS before and after BTX injections; these studies disclosed an altered corticomotor representation in dystonia patients, which could be reversed by BTX injections.[19] Likewise, a recent study established a decrease in intracortical inhibition in patients with dystonia, which could be normalized by BTX.[20] Conversely, cortical excitability studies with PET in patients with writer's cramp did not show an effect of BTX in the primary motor cortex and premotor area.[21] Moreover, in another PET study, in patients with BSP before and after local injections with BTX, there were no significant differences between pre- and postinjection findings in any of the studied regions.[22] Recently, the effects of BTX on motor system excitability in patients with writer's cramp were studied with

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electrophysiologic techniques; as in the PET studies, there were no significant changes following BTX injections.[23]

Differently from other focal dystonias, the upper facial territories constitute the best body segment for an examination of cortical excitability because the SP recorded from these muscles originates solely in the cortex.[24,25] We have studied, before and after BTX-A injections, the SPs induced by single-pulse high-intensity TMS. This method has already been proven to be useful in detecting abnormal shortened cortical silent periods in the orbicularis oculi muscles of patients with cranial dystonia.[26] A change in cortical motor excitability would indicate a direct effect of BTX on the CNS unrelated to its action on the neuromuscular synapse or other peripheral mechanisms.

MATERIALS AND METHODS

Subjects

Ten patients with cranial dystonia (age range 39 to 79 years) and 7 age-matched control subjects (age range 38 to 76 years) participated in the study. Informed consent was obtained from all participants, and the study was approved by the local Ethics Committee. Patients were also grouped according to the distribution of cranial dystonia: patients with blepharospasm alone (n = 4; mean age 65 years) and those with blepharospasm plus oromandibular dystonia (n = 6; mean age 69 years).

Botulinum Toxin Treatment

All patients were receiving regular botulinum toxin injections (on average every 3 or 4 months), and all were studied at least 4 months after the last injection. Patients were studied before and 2 to 3 weeks after the injection of BTX-A into the affected muscles. BTX-A (Botox; Allergan, Irvine, CA) was injected at a dose ranging from 50 to 100 mouse units depending on the severity of the dystonia. None of the patients received concurrent medication with anticholinergics, neuroleptics, or benzodiazepines for at least 4 weeks before the study.

Clinical Assessment

Efficacy of treatment was assessed by a global improvement scale, estimated at the "peak effect" of BTX injection (0, no effect; 1, mild effect but no improvement in function; 2, moderate improvement, but no change in functional disability; 3, moderate improvement in severity and function; 4, marked improvement in severity and function). We considered that a patient had improved when the score reached 3 or 4 after treatment.

Transcranial Magnetic Stimulation

Stimuli were delivered by a Dantec Maglite® magnetic stimulator (Skovlunde, Denmark) connected to a round coil (outer diameter 12 cm) placed over the vertex. The coil was placed so that the side where current flowed clockwise faced upwards. The intensity of stimulation was as close as possible to maximum stimulator output, depending on subject tolerance (range 90% to 100%).

Recording Technique

EMG responses were recorded from surface electrodes placed over the left orbicularis oculi muscle. The level of muscle activation was monitored on line on a screen (gain 50 μV/division) with audio feedback. EMG activity was recorded and stored for off-line analysis on a Nihon Kohden® eletromyograph (Japan). Signals were amplified and filtered (bandpass 200 to 2000 Hz) and full-wave rectified. Background EMG activity was recorded for 200 milliseconds before delivering the magnetic stimuli. Patients and control subjects were asked to contract the target muscles at their maximum strength.

Silent Periods

Stimulus intensity was increased in 10% steps from 30% to 100% of maximum stimulator output, so that subjects could tolerate higher intensities. At the highest tolerable intensity for each subject (either 90% or 100%), 5 silent periods were recorded and averaged. The duration of the SP was measured from the end of the MEP to the latency at which the EMG activity returned to its mean prestimulus level.

Statistical Analysis

The Wilcoxon Signed Ranks Test was used to evaluate differences between pre- and post-BTX-A SP durations. The Mann-Whitney *U*-test was carried out for control versus pre-BTX-A comparison. The level of significance was set at 99% (0.01).

RESULTS

All patients had a moderate to marked improvement of their symptoms, according to the clinical scale, and reported weakness in the injected muscle. A total dose of 50 to 100 units of BTX was injected into the affected muscle in our patients. In all control subjects, high-intensity TMS resulted in cortical SPs comparable to those found in another study performed on upper facial muscles.[26] SPs had shorter durations in patients than in normal subjects ($P = 0.001$) (Figs. 1–3). Following BTX injections, TMS revealed no significant difference ($P = 0.560$) between SPs before and after treatment (Fig. 4).

DISCUSSION

The neurophysiological studies performed in our patients evaluated inhibitory intracortical processes; they demonstrate decreased inhibition of motor cortical interneurons engaged in SP response to TMS in all dystonic patients when compared with normal subjects. Our findings are in agreement with a previous study in patients with cranial dystonia[26] and primary dystonia.[4]

In our patients, local injections of BTX induced clinical functional improvement and a significant relief of muscle spasms. However, the physiologic abnormalities described above were not modified. Instead, they continued to be as abnormal at the time of the patient's greatest clinical improvement as they were before treatment.

Possible changes in cortical excitability after BTX injections may have numerous mechanisms, including a direct

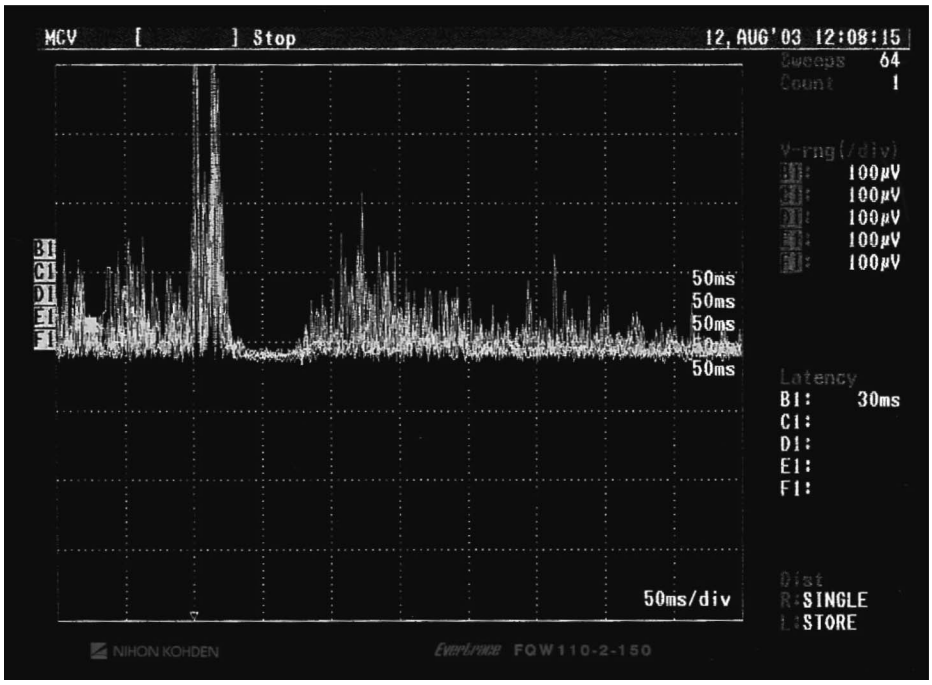

FIGURE 1. Representative figure of silent periods obtained in the patient group, with 5 superimposed, rectfied traces.

action of BTX at the central level, because BTX may reach the CNS either through the bloodstream and the blood–brain barrier[27] or by retrograde transport through motor fibers and propriospinal pathways.[28–30] In animal models, only at high doses of BTX did CNS actions become apparent.[14] In contrast, only low doses were used in our study, and that also argues against any central effects. The second point is that intracortical inhibitory mechanisms are GABA mediated, whereas botox acts mainly on cholinergic nerve terminals.[14,31] Previous studies using BTX injections in overactive muscles of patients with upper limb dystonia have demonstrated cortical excitability changes and restoration of intracortical inhibition,[20] thus suggesting that changes in muscle afferent input might lead to motor cortical reorganization. Nevertheless, unlike limb muscle SPs, facial muscle SPs originate solely from intracortical inhibitory mechanisms.[24,25] Facial muscles do not act on joints, they have few or no proprioceptors, and their motoneurons neither undergo reciprocal inhibition nor possess the axonal collaterals needed to receive recurrent inhibition,[32–35] and for that reason modulations in afferent input are unlikely to

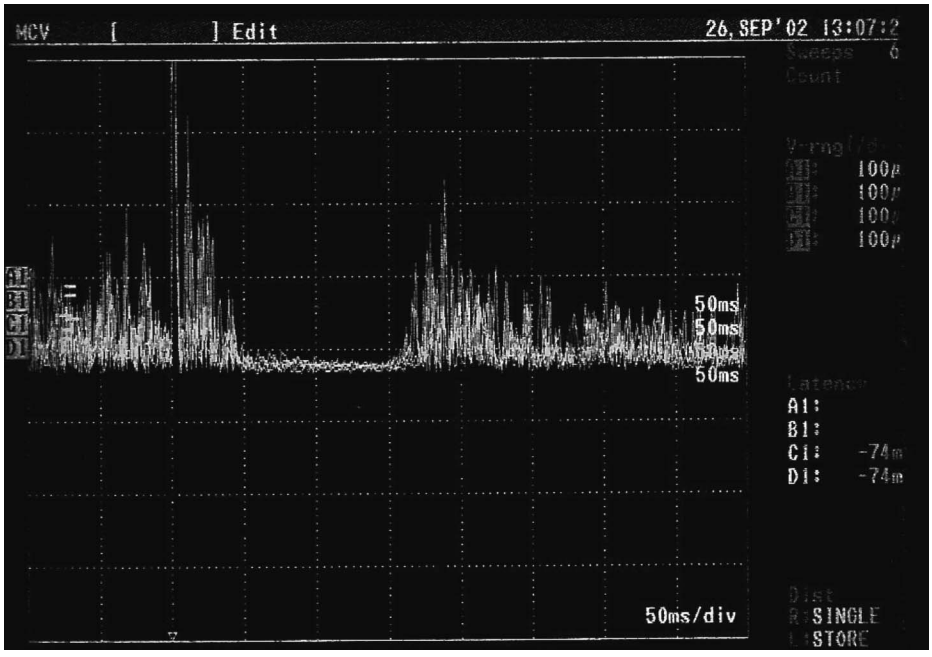

FIGURE 2. Representative figure of silent periods obtained in the control group, with 5 superimposed, rectfied traces.

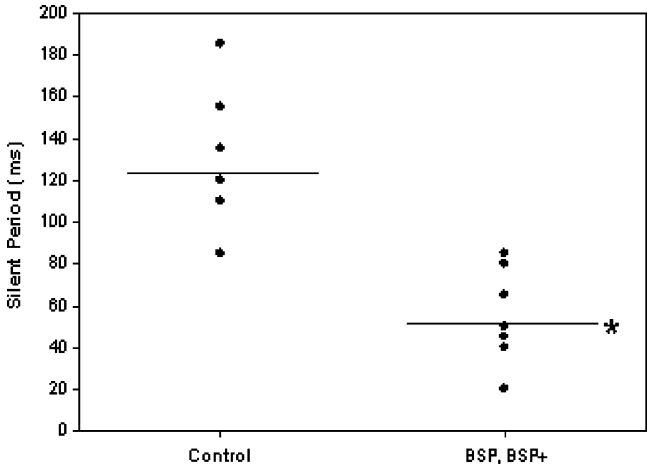

FIGURE 3. Comparison of SP values in controls and BSP patients (some data points are superimposed). *$P < 0.01$.

have influenced changes in cortical excitability. Even in upper limb muscles, however, changes in cortical excitability may not be present, as has been demonstrated by Hallett et al[23] and Ridding et al[36]; these authors did not find any significant changes in intracortical inhibition before and after BTX injections in "focal" hand dystonia, suggesting that any beneficial effects are mainly caused by BTX's peripheral actions on the neuromuscular junction.

In addition, some trigger factors appear to initiate blepharospasm (BSP) in individuals genetically or environmentally predisposed to dystonia. The predisposing condition in a rat model of BSP[37] is a 30% unilateral loss of dopamine-containing neurons in the substantia nigra pars compacta. In the presence of reduced inhibition within trigeminal blink circuits created by such dopamine loss,[38] an additional weakening of the orbicularis oculi (OO) muscle triggers spasm of lid closure and other characteristic symptoms of BSP. Recent studies have examined how OO weakening might be a trigger for BSP.[39–41] Should this model be true, facial weakness might lead to an increase in CNS excitability; one could then expect worsening of blepharospasm after BTX injections and its induced muscle weakness.

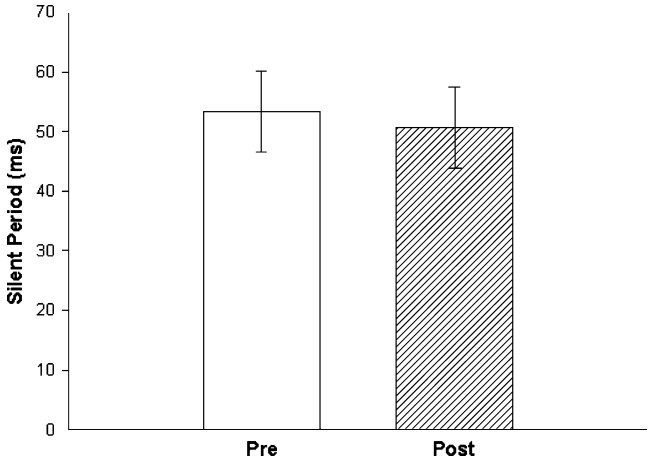

FIGURE 4. Comparison of mean SP values in BSP patients before and after BTX injections.

From clinical experience, we know that treatment with BTX injections in the OO undoubtedly improves most patients and in our case does not appear to change cortical SPs in treated patients. Likewise, previous neurophysiological studies have demonstrated that BTX use in patients with dystonic blepharospasm weakens the OO muscle but does not change brainstem interneuronal excitability.[18] We believe that muscle weakness may play a role in the initiation of BSP, but a further weakening of the involved muscles does not seem to aggravate this condition or to have any effects in central excitability.

Finally, recent studies with intramuscular injections of [^{125}I]botulinum neurotoxin complex in the eyelids of rabbits and gastrocnemius muscle of rats indicate that most of the neurotoxin does not diffuse from the injection site, and almost no radioactivity was recovered from the brain.[42]

We conclude that the clinical improvement induced by BTX in patients with cranial dystonia is largely symptomatic and does not seem to involve excitability changes of cortical motor areas from reorganization of inhibitory intracortical circuits.

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