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Botulinum Toxin and Neuromotor Rehabilitation: An Integrated Approach to Idiopathic Cervical Dystonia

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Abstract: Currently, the best treatment option for idiopathic cervical dystonia (ICD) is injection of botulinum toxin (BTX) into the affected muscles, whereas rehabilitative approaches have given disappointing results. We evaluated whether the association of an ad hoc rehabilitative program may improve the clinical efficacy of BTX treatment in a single-center, cross-over, controlled study. Forty patients with ICD were randomly assigned to two different treatment groups: (1) BTX type A (BTX-A) plus a specific program of physical therapy (BTX-PT) or (2) BTX-A alone (BTX-0). Patients in the BTX-PT group showed a longer duration of the clinical benefit (118.8 vs. 99.1 days) and needed a lower dose of BTX at reinjection (284.5 vs. 325.5 units). In addition, they showed more marked reductions in their disability in activities of daily living (–9.7 vs. –4.85 points) and subjective pain (–13.35 vs. 6.95 points) scores. Association of BTX-A therapy with a specific program of physical therapy may improve ICD treatment outcome. © 2006 Movement Disorder Society

Key words: botulinum toxin; cervical dystonia; physiotherapy; biofeedback

Idiopathic cervical dystonia (ICD) is the most widespread form of primary dystonia,¹ which presents with abnormal postures of the neck² and neck pain.^{3,4} The effectiveness of oral medications in the treatment of this disabling condition is still far from proven, and the

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TABLE 1. Population characteristics

	First BTX-PT (20 patients)	First BTX-0 (20 patients)
Sex (M/F)	7/13	6/14
Age in years (mean \pm SD)	50.6 \pm 16.6	52 \pm 14.6
CD duration in years (mean \pm SD)	7.3 \pm 2.8	6.5 \pm 3.1
CD type		
mono morphology	12	13
mixed form	8	7

BTX-PT, botulinum toxin in combination with physical therapy; BTX-0, botulinum toxin therapy alone; CD, cervical dystonia.

neurosurgical approaches proposed so far should be considered investigational, given that they have not been the subject of controlled studies and their long-term effects are unknown.⁵

Currently, the best treatment option, supported by convincing evidence of efficacy, is the injection of botulinum toxin type A (BTX-A) into affected muscles.^{6–8} The beneficial effect of BTX-A typically appears within a few days of injection and lasts for 3 to 6 months. BTX-A treatment, however, may present several limitations. Repeated reinjection carries the potential risk of provoking an immune reaction that may result in unresponsiveness to BTX-A.^{7,8} In addition, it was demonstrated recently that the dosage of BTX-A needs to be increased progressively to prolong its effectiveness.⁹ Furthermore, in some patients, a lateral or anterior/posterior shift is also important and especially difficult to treat with BTX.

Attempts to rehabilitate patients with ICD have been inconclusive,¹⁰ although, in some cases, promising.¹¹ In the present study, we sought to evaluate whether the association of an ad hoc rehabilitative program with BTX treatment might improve the clinical efficacy of the latter, measured in terms of pain control, range of motion of muscles, postural control, dose, and quality of life.

PATIENTS AND METHODS

A total of 40 patients (13 men and 27 women; mean age, 51.3 \pm 15.6 yr), who had suffered from ICD for at least 3 years and who had responded previously to at least two BTX-A injections (the last dose administered at least 6 months before enrolling), were selected for this single-center, cross-over, randomized controlled study (Table 1). The study protocol was approved by the local ethics committee, and written informed consent was obtained from all the patients. The patients were randomly assigned into two treatment arms: BTX-0 group (BTX-A injection alone) or BTX-PT group (BTX-A injection

followed immediately by a specific rehabilitation program). The patients were subsequently crossed over after an interval of 45 to 120 days (observation period), which depended on the duration of the subjective clinical benefit and was confirmed by the electromyographic (EMG) evaluation (dystonic activity comparable to baseline). Patients were instructed to promptly contact their doctor by phone, when they deemed the effect of BTX-A was over, to schedule a visit and an EMG examination within 48 hours.

Each patient was treated with BTX-A by a neurologist with much experience in the treatment of dystonia with BTX (F.M.), who was blind to the study phase. BTX-A was injected into one or more of the following muscles, depending on the clinical picture and on the presence of dystonic activity at needle EMG: sternocleidomastoid, splenius capitis, scalenus, rectus capitis, semispinalis capitis, and trapezius. Needle EMG was used to measure the amplitudes of dystonic and maximal voluntary activities in neck muscles and to distinguish genuine dystonic muscle coactivation from compensatory muscle activity. In each muscle, a dose of 100 to 200 U of BTX-A was delivered, on the basis of each muscle size and hyperactivity, as detected by EMG, and of previous response to BTX treatment. The maximum amount of BTX-A allowed was 500 U/patient, based on personal experience, recently confirmed by data from the literature.⁸ BTX-A was injected using a 30-gauge needle under EMG guidance.

Immediately after BTX administration, patients in the BTX-PT group began a specific PT program based on daily sessions lasting 60 to 90 minutes each for 2 weeks. The PT duration of 2 weeks was arbitrarily chosen in accordance with literature data on the latency of appearance of initial and maximal response to pharmacological denervation with botulinum toxin in the 4 weeks after injection.^{9,12} In addition, we opted for a relatively short PT protocol to minimize the possible confounding effect related to the disparity in treatment intensities (BTX alone vs. BTX + PT). The PT program included two initial sessions of 60 minutes based on passive myofascial elongation maneuvers and deep massage of cervical muscles. Subsequent sessions comprised 20 minutes of passive myofascial elongation maneuvers, 20 minutes of active stretching to increase the range of motion of muscles, tendons, and ligaments, and 20 minutes of exercises to improve postural control and balance, and to strengthen the axial musculature. Biofeedback training was also used (approximately 30 minutes per session) as an additional tool, according to the procedure described by Smania and colleagues¹¹ for increasing the effect on residual neck and shoulder muscle contraction as well as for teaching exercises.

Cervical dystonia was assessed by neurological examination, using validated scales to evaluate severity of disability (Tsui scale and Toronto Western Spasmodic Torticollis Rating Scale [TWSTRS]) and disability in activities of daily living (ADL).^{13,14}

Subjective pain was recorded in terms of (a) *intensity* (0 [absence of pain] to 10 [worst pain ever]; (b) *duration*, on a six-point scale graded from 0 to more than 75% of the day; and (c) *pain-related disability* (0 [no pain-related disability] to 5 [pain is the sole cause of my disability]). The sum of the scores recorded in subitems a, b, and c gave the Total Pain score.

The patients were assessed at baseline and at the end of each observation period. The primary outcome measures were represented by the changes in Tsui scale, TWSTRS, ADL, and Total Pain scores in response to the different treatments. Secondary endpoints were the effect of treatments upon the subsequent dose of BTX and the duration of the interval between the first and the second treatment.

Statistical Analysis

An analysis of variance (ANOVA) model was used to assess sequence-related effects. Treatment effect was evaluated by comparing the two groups (BTX-0 vs. BTX-PT) for score changes (in the above scales) versus baseline, doses of BTX-A injected per session, and time between two consecutive BTX-A injections. In this way, each patient served as his/her own control. Two-way ANOVA for repeated measures, Student's *t* test and Mann-Whitney test were used as required.

RESULTS

All the patients included in the study showed a complete compliance to the protocol proposed. The baseline characteristics of the subjects did not differ significantly between the two treatment groups (Table 1). No carryover effect was observed with regard to the sequence of treatments on the main outcome measures. After BTX-A injection, patients in all groups experienced a reduction of pain and improved neck movements, with a significant improvement in all the scales adopted ($P < 0.001$). No significant differences among groups were observed with regard to the improvements recorded on the Tsui scale and the TWSTRS (Table 2). Conversely, the improvements recorded on the scales assessing ADL and Total Pain score were significantly greater in the patients who underwent BTX-PT, irrespective of the treatment sequence, than in those who underwent the BTX-0 treatment. In addition, when BTX-PT treatment was given first, the benefit lasted longer than when BTX-0 treatment was given first (119 days vs. 99 days;

TABLE 2. Effect of botulinum toxin type A alone or in combination with physical therapy on different scales

Parameter	BTX-0	BTX-PT
Tsui scale	-8.1 ± 3.2	-7.2 ± 2.8
TWSTRS	-9.1 ± 6.8	-10.2 ± 6.0
ADL	-5.3 ± 5.2	-9.8 ± 6.3 ^a
Total Pain score	-7.1 ± 3.2	-13.0 ± 3.2 ^b

See text for further details. Data are expressed as mean differences (\pm SD) between baseline scores and scores recorded at the end of each observation period.

^a $P < 0.05$.

^b $P < 0.001$.

BTX-PT, botulinum toxin in combination with physical therapy; BTX-0, botulinum toxin therapy alone; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; ADL, activities of daily living.

$P < 0.05$). When comparing the doses used in the second treatment period versus the first period, the group of patients who underwent the combined treatment (BTX-PT) first required a significantly lower dose of BTX-A for the second treatment than those undergoing the reverse schedule (i.e., BTX-0 followed by BTX-PT; -60 vs. -19 U; $P < 0.01$).

No subjects complained of symptoms exacerbations during the PT protocol, nor manifested unwillingness to return to the hospital after physiotherapy. Adverse events were infrequent and mild (transient dry mouth and neck muscle weakness) in both groups.

DISCUSSION

The treatment of ICD has been unsatisfactory for decades, although it has improved considerably since the introduction of botulinum toxin, which is nowadays considered the most effective symptomatic treatment for this condition.^{6,8} Clinical experience gathered over years treating ICD patients at our Institute has prompted the idea that a PT program might be a valid complementary tool, in addition to BTX-A, for treating ICD patients. This strategy was also suggested by the demonstration that muscular activation seems to be associated with an increase in the clinical effectiveness of botulinum toxin.¹⁵

The present randomized, controlled, cross-over study demonstrated that the association of a rehabilitative program to BTX-A treatment increases the beneficial effect of this later and allows the use of lower doses, thus possibly resulting in a reduction of the risk of developing immune-mediated unresponsiveness to BTX-A.

In both groups, BTX-A proved effective in controlling ICD symptoms, but the BTX-PT protocol produced an additional, significant decrease in perceived pain and an increase in ADL functioning. The better performance in pain scores may be interpreted as a consequence of a more marked reduction in muscle contraction and abnor-

mal posture. Teaching patients how to control their posture and muscle contraction, also through the introduction of biofeedback techniques, may help to keep pain levels under control and, thus, reduce disability in ADL.

Further studies are necessary for confirming this speculation, as well as for attempting to isolate the effect of physiotherapy from that of biofeedback and for testing the potential increase in efficacy with a longer PT protocol. Nonetheless, the present data strongly suggest that associating a specific rehabilitative program with BTX-A therapy may represent a valid approach that improves ICD treatment.

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Computerized Posturography Balance Assessment of Patients With Bilateral Ventralis Intermedius Nuclei Deep Brain Stimulation

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Abstract: Bilateral ventralis intermedius nuclei (Vim) deep brain stimulation (DBS) improves tremor in patients with both essential tremor (ET) and Parkinson's disease (PD). In each condition, patients have individually noted both subjective improvement and worsening in balance. Computerized posturography (CP) is able to quantify some aspects of balance. Twenty-one patients (8 with PD and 13 with ET) with bilateral Vim DBS were recruited to undergo randomized-order identical CP testing (EquiTest system) while their DBS devices were both activated and deactivated. One PD patient could not complete any OFF assessment and is not included. Three PD patients could not tolerate portions of the OFF testing. Overall, sensory organization testing was improved by DBS activation in conditions that involved quiet standing with eyes open with no motion of the support surface, or with sway-referenced support surface motion, but worsened during quiet standing with eyes closed only in ET patients. Falls lessened with activation in ET patients. Motor control testing was not changed. Bilateral Vim DBS activation mostly improved balance, but may modestly worsen other specific features. © 2006 Movement Disorder Society

Key words: essential tremor; Parkinson's disease; ventralis intermedius nuclei deep brain stimulation; thalamic stimulation; computerized posturography

Gait and balance difficulties, as measured by computerized posturography (CP), are seen in both Parkinson's disease (PD) and essential tremor (ET). CP results vary somewhat in PD but in general, medium latency perturbations are abnormally high¹ and long latency responses are poorly adaptive.² Sensory organization testing is often abnormal. They variably improve with dopaminergic medications and surgical interventions.^{3–5} ET patients show modest abnormalities in CP^{6,7} and also have im-

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