Influence of Botulinum Toxin Type A Treatment of Elbow Flexor Spasticity on Hemiparetic Gait

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CME Objectives:

Objectives: Upon completion of this article, the reader should be able to 1) understand the rationale for treating the patient with upper-limb spasticity and muscle overactivity with botulinum neurotoxin to improve gait function; 2) describe expected improvement in gait functioning in this patient group after botulinum neurotoxin injection to the spastic upper limb; and 3) identify areas for future research studies to evaluate improving gait function by treating the upper limb.

Level: Advanced.

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Influence of Botulinum Toxin Type

A Treatment of Elbow Flexor Spasticity on Hemiparetic Gait

ABSTRACT

Esquenazi A, Mayer N, Garreta R: Influence of botulinum toxin type: a treatment of elbow flexor spasticity on hemiparetic gait. Am J Phys Med Rehabil 2008; 87:000–000.

Objective: To assess whether walking velocity could be improved in patients with disorders related to upper–motor neuron syndrome (UMNS) by treating elbow flexor spasticity with botulinum toxin type A (BoNTA).

Design: This was a prospective, open-label, multicenter, interventional evaluation. The study group of 15 patients (mean age, 51.3 yrs; ten men, five women) were independent ambulators with residual hemiparesis attributable to stroke or traumatic brain injury of at least 18-mo duration. Patients were injected with 120–200 units of BoNTA (BOTOX, Allergan, Inc., Irvine, CA) to the affected biceps, brachialis, and/or brachioradialis. Modified Ashworth scores and gait velocity were assessed before and after BoNTA treatment. An untreated control group was employed to assess the potential impact of time on test–retest reliability of the selected temporal spatial gait parameters.

Results: The BoNTA group demonstrated a statistically significant increase in walking velocity from 0.56 m/sec before treatment to 0.63 m/sec after treatment ($P = 0.037$). The mean modified Ashworth score was significantly reduced from 2.6 before BoNTA treatment to 1.4 after treatment ($P = 0.00, 0.003$).

Conclusions: Treatment of upper-limb spasticity may be an important adjuvant treatment for patients with gait disturbance related to the UMNS.

Key Words: Spasticity, Botulinum Toxin Type A, Gait

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Normal gait patterns are an expression of well-coordinated movements of many upper- and lower-limb segments as well as the trunk, head, and neck.[1,2] During normal walking, the upper limbs move synchronously with the lower limbs, each arm alternately swinging in phase with its contralateral lower limb.[3] The coupling of upper- and lower-limb movements influences walking velocity.[4,5] Stride length increases with walking velocity and is normally accompanied by a proportional increase in arm swing amplitude.[6,7] Normal arm swing patterns influence postural control of the body and, thereby, the efficiency of gait[7] and the maintenance of body equilibrium.[1] In one study, deliberate changes in arm swing patterns caused significant gait disturbances.[7] Arm swing patterns and walking velocity are thus mutually dependent and, in combination, influence gait. Therefore, reciprocal arm swing is an important feature that can affect gait parameters. Furthermore, the common clinical observation that patients with spastic hemiparesis have impaired or absent reciprocal arm swing during walking suggests the possibility that the upper limb in such patients may be influencing other gait parameters as well.

A review of the literature reveals that hemiparetic patients with spasticity and other forms of muscle overactivity have limited arm movement, resulting in restricted arm swing,[8] which has been linked to decreased gait efficiency, particularly at lower walking speeds.[9] Interestingly, a paretic upper limb treated with electrical stimulation has been correlated with improved gait parameters, highlighting the potential influence of "remote" upper-limb motor deficits on gait.[7] Hirsch et al.[10] report that treatment of the hemiparetic upper limb attributable to stroke with botulinum toxin type A (BoNTA; DYSPORT, Ipsen Ltd., UK) correlated with improvement of several parameters of gait, including stride time and ankle and knee range of motion. A number of our own patients reported to us that they walked better and faster after they were treated with focal chemodenervation in the upper extremity. However, in our opinion, the relationship between treatment of upper-limb muscle overactivity and subsequent changes in gait has not been studied enough. In particular, walking velocity, influenced by interlimb coordination and symmetry,[11–13] and also used as a basic variable when evaluating gait of patients with the upper–motor neuron syndrome (UMNS),[14] has not been studied sufficiently. In a clinical context, improved walking velocity is considered an important outcome measure of rehabilitation and a marker of recovery in patients with UMNS residuals.[13,14] Therefore, on the basis of literature reports describing changes in gait associated with focal chemodenervation of upper-limb muscles, we undertook the present study to determine whether treatment of spastic elbow flexors with BoNTA could be linked to an increase in self-selected "comfortable" speed and self-selected "fast as possible" speed of walking in patients with an UMNS.

METHODS

Design

This was a prospective, open-label, multicenter study conducted from May 2002 to March of 2005. Patients were evaluated in one of two gait laboratories in a rehabilitation hospital using the same protocol and instrumentation. The study was approved by local research ethics committees.

Participant Characteristics

Eligible participants were patients diagnosed with cerebral vascular accident or TBI resulting in UMNS and elbow flexor muscle overactivity. Patients' unilateral elbow flexion posture had to be amenable to BoNTA treatment to one or more muscles, and at least 18 mos had to have elapsed since the neurological event. Patients' ambulation had to be characterized as independent with or without assistive devices, and their pharmacological spasticity regimen had to be stable. Patients who had surgery or BoNTA injections of the lower limbs within 6 mos of enrollment in this study were excluded.

Intervention

Each vial of BoNTA (BOTOX) was stored in a refrigerator at 2–8°C before use and contained 100 U of BoNTA, 0.5 mg of albumin (human), and 0.9 mg of sodium chloride in a sterile, vacuum-dried form without a preservative. Each vial of BOTOX was reconstituted with 2 ml of 0.9% sterile, preservative-free saline.[15]

Patients were administered a total BoNTA dose ranging between 120 and 200 U to the affected arm. Muscles included were the biceps, brachialis, or brachioradialis, according to individual need as determined by the investigators' clinical judgment. Maximum dose for the biceps was 120 U, for the brachialis 60 U, and the brachioradialis 80 U. No more than 50 U were injected in the same site, and EMG or electrical stimulation guidance through the injecting needle was used in all cases to confirm localization in the desired muscle.

Outcome Measures

Modified Ashworth scores (MAS) were used to measure BoNTA treatment effect on elbow spasticity, and selected temporal spatial walking data were obtained before and 2–12 wks after BoNTA treatment. Patients were provided standardized verbal instructions regarding ambulation on the Gait Mat (GaitMat II, E.Q. Inc, Chalfont, PA). The Electronic GaitMat II is an instrumented walkway, 3.8 m long, which contains approximately 10,000 electronic switches, scanned at 100 Hz. Subjects walk over the mat, which is mounted flush with the floor. A recording of foot contact generates a timed "electronic footprint," which provides data about walking speed and other gait parameters.

Temporal spatial data were analyzed on the basis of an average of at least ten steady-state strides from the Gait Mat. Data were recorded under two conditions: walking at self-selected "comfortable" speed in meters per second, and walking at self-selected "fast as possible" speed. Most hemiparetic patients function within a narrow range. The recording of these two measurements is an attempt to determine each patient's approximate functional capacity range. The first and last steps over each pass of the Gait Mat were not used. Patients were evaluated on the Gait Mat to obtain baseline values of their temporal spatial walking parameters before treatment with BoNTA. Potentially confounding variables such as medications and/or therapy regimens were not controlled.

Patients returned to the gait lab for follow-up evaluation between 2 and 12 wks (mean 6.8 wks) after BoNTA treatment was administered. The maximal effect of BoNTA is generally evident from weeks 2–8 after treatment, but the effects can last as long as 20 wks. The protocol and condition for data collection of the follow-up evaluation were identical to those of the initial evaluation.

An age-, condition-, and time-matched control group of ten patients (five men and five women, with similar diagnostic and functional characteristics to the BoNTA-treated patients) was tested for walking velocity, using the same instrumentation at similar intervals to test whether merely walking on the Gait Mat or the time interval between evaluations, or a learning effect or familiarity with the environment and equipment, were sufficient to produce a change in walking velocity. These patients did not receive BoNTA or sham treatment.

Statistical Analysis

Descriptive statistics (means and standard deviations) were used to analyze the temporal spatial data before and after BoNTA treatment. Paired *t* tests were run to assess the differences in walking velocity, and the Mann–Whitney *U* test was used to assess the modified Ashworth scores before and after BoNTA treatment. A correlation coefficient of these parameters was also done, and the nonparametric Wilcoxon signed rank test was used to assess the differences in walking velocity and Ashworth scores.

RESULTS

Patients

A total of 15 patients (mean age 51.3 yrs; ten men, five women) were administered BoNTA to the elbow flexors. These patients had hemiparesis (right side, $n = 7$; left side, $n = 8$) as a result of stroke or TBI, and all were able to ambulate independently with or without an assistive device or brace. The control group for purposes of test–retest reliability was age-, diagnosis-, and functional level matched ($n = 10$; mean age 54.8 yrs; five men, five women). The mean elapsed time for follow-up gait evaluation was just under 7 wks (6.8 wks).

Temporal–Spatial Walking Parameters

The BoNTA-treated group demonstrated a statistically significant increase in steady-state self-selected comfortable walking velocity from 0.56 m/sec before treatment to 0.63 m/sec after treatment ($P = 0.037$, *t* test; Fig. 1). The nonparametric test showed less sensitivity to the differences in walking velocity ($P = 0.064$, Wilcoxon signed rank test). No change in fastest possible walking velocity was evident for the BoNTA group. No statistically significant change in the self-selected comfortable walking velocity or fastest possible walking velocity was evident in the untreated control group, indicating good test–retest reliability.

F1

Modified Ashworth Score

BoNTA treatment resulted in a statistically significant reduction in the mean modified Ashworth

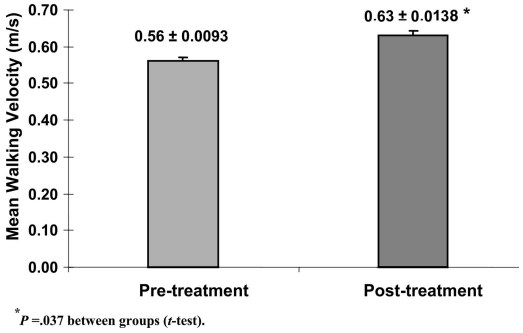

FIGURE 1 *Change in self-selected comfortable walking velocity.* *P = *0.037 between groups (*t *test).*

score of the elbow from 2.6 before BoNTA treatment to 1.4 at 2–12 wks after treatment (P = 0.00,003).

Safety and Tolerability

No adverse events or undesirable effects were reported by the group of patients who received BoNTA.

DISCUSSION

Using nonparametric statistics, a significant change in modified Ashworth scale for the elbow flexors was observed after treatment with BoNTA. Technically, if a patient is known to be spastic, the MAS does not solely measure the patient's spasticity. Rather, it measures all sources of resistance to passive stretch, reflexive *and* rheologic. Patients were included in this study when traditional testing of the elbow flexors at different velocities of stretch indicated that the patient was, indeed, spastic. Once a patient was diagnosed as spastic, the MAS was used to quantify muscle "tone," which, to us, means the resistance to stretch whose components can include spastic stretch reflex activity as well as physical or rheologic resistance of muscle and other soft tissues. We do think that BoNTA, considering its well-documented blocking action at the neuromuscular junction that affects subsequent muscle contraction, alters the reflex contraction component of muscle tone. Hence, we argue that the observed change in MAS after BoNTA treatment reflects a reduction in stretch reflex activity, even though the absolute MAS score represents static rheologic properties as well as dynamic reflex properties of the muscles involved. We believe that a change in MAS almost certainly reflects a change in the tension contributed by the stretch reflex or spasticity.

Focal chemodenervation was also linked to a change in patients' ambulation, specifically their chosen comfortable walking velocity. The matched control group of patients did not show a change in walking velocity, suggesting that merely walking on the Gait Mat or the interval time between evaluations was not sufficient to lead to changes in this parameter. BoNTA treatment did not result in significant changes in fastest possible walking velocity. The results of this preliminary study suggest that effective treatment of elbow flexor spasticity with BoNTA seems to correlate with a statistically and clinically significant increase in self-selected comfortable walking velocity. The observed increase of 0.07 m/sec would improve an individual's ability to safely cross a roadway, which is particularly important in urban settings. A reduction in muscle overactivity in one part of the body, in this case the elbow flexors, may also reduce excitability of the central nervous system in movement-related activities of other limbs, with resulting functional improvement of clinical significance.

Several studies suggest that BoNTA affects the functional organization of the central nervous system indirectly through peripheral mechanisms.[16–19] BoNTA may alter spindle afferent inflow directed to spinal motoneurons or to various cortical areas, thereby altering spinal as well as cortical mechanisms.[20] Muscle afferent input is tightly coupled to motor cortical output, so that the afferents from a stretched muscle innervate cortical areas where they can excite neurons capable of contracting the same muscle.[20]

The exact mechanisms for the relationship between effective treatment of arm spasticity and improved gait need to be further elucidated, but they may be linked to the coupling patterns of arm and leg movements, which influence walking velocity.[4] BoNTA treatment of muscle overactivity in the lower extremity of a hemiparetic patient improved walking velocity and several other gait parameters and led to a more efficient gait pattern.[21] Normal gait consists of an interaction between all of the extremities, with the legs alternating contact with the ground and the arms swinging freely to produce forward momentum of the body. For normal gait to occur, the feet have to move forward in a coordinated movement synchronous with the knees, hips, spine, arms, shoulders, and head to maintain balance and achieve controlled forward motion involving coordinated and precisely timed muscle interactions.[5]

UMNS interrupts the normal biomechanical balance between the upper and lower extremities during movement, resulting in an increase in energy expenditure during movement that is usually followed by a compensatory decrease in walking velocity.[5]

The efficacy of BoNTA in treating patients' upper-limb spasticity may explain the observable increase in walking velocity of the patients in this study. Effective treatment of upper-limb muscle

overactivity may, therefore, improve arm swing and help improve gait efficiency, particularly at lower walking speeds.[9] BoNTA has a well-established clinical profile as a safe, effective focal treatment of upper-limb and lower-limb muscle overactivity.[22–27] It is important to note that the potential for BoNT-mediated improvement should be assessed in the context of other problems common to the patients with UMN disorders, such as loss of muscle strength or abnormal motor patterns.[28–30]

The interpretation of the study results is limited by several factors. The relatively few patients analyzed, and the fact that this was an open-label design study, should be considered when interpreting the results. The clinical presentation of muscle overactivity in multiple joints may vary with each patient, and the time since neurological injury may also influence the pattern of presentation. UMNS-related spasticity changes with stress or general disease and also with postural changes. In addition, variability in gait is common in patients with UMNS-related disorders. The sample size of our patient population may therefore exhibit a level of variability that makes definitive interpretation of the results difficult. We selected our subjects from those at least 18 mos from time of neurological injury. Arm swing improvements were not quantified, there were no controls for potentially confounding factors such as concurrent medication and the use of other types of therapy, and between-group analyses were not performed. Finally, improvement was noted only on self-selected "comfortable" walking velocity. Effective BoNTA treatment of UMNS-related muscle overactivity of elbow flexors or perhaps other involved muscle groups may improve patients' overall gait, but this needs to be evaluated in larger, controlled trials.

The exact influence of muscle overactivity in gait disorders associated with UMNS patients is clinically difficult to assess. Measuring the effect of treating muscle overactivity may clarify its role in gait disorders. A randomized, placebo-controlled future study that involves collecting full-body kinematic data during ambulation as well as temporal–spatial parameters of walking and controlling for potentially confounding factors is proposed. Dosing and results reported in this study are specific to the formulation of botulinum toxin type A (BOTOX) manufactured by Allergan, Inc. (Irvine, CA).

CONCLUSION

This study shows that BoNTA treatment of overactive elbow flexor muscles leads to significant improvements in self-selected walking velocity. Supported by findings of this study, the perception reported by patients of improvement in gait after treatment of upper-limb muscle overactivity is present and may be an important adjuvant treatment for patients with gait disturbance related to the UMNS.

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