ORIGINAL ARTICLE

Time Course Analysis of the Effects of Botulinum Toxin Type A on Elbow Spasticity Based on Biomechanic and Electromyographic Parameters

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ABSTRACT. Lee H-M, Chen J-JJ, Wu Y-N, Wang Y-L, Huang S-C, Piotrkiewicz M. Time course analysis of the effects of botulinum toxin type A on elbow spasticity based on biomechanic and electromyographic parameters. Arch Phys Med Rehabil 2008;89:692-9.

Objective: To quantify changes of elbow spasticity over time after botulinum toxin type A (BTX-A) injection in the upper extremity of stroke patients.

Design: Before-after trial in which the therapeutic effects were followed up at 2, 6, and 9 weeks after the BTX-A injection (Botox).

Setting: Hospital.

Participants: Chronic stroke patients (N=8) with upper-limb spasticity.

Intervention: BTX-A was injected in upper-limb muscles, including the biceps brachii.

Main Outcome Measures: Treatment effects were quantified as the changes in the velocity and the length dependence of hyperexcitable stretch reflexes. Manual sinusoid stretches of the elbow joint at 4 frequencies (1/3, 1/2, 1, 3/2Hz) over a movement range of 60° were performed on patients by using a portable device. The Modified Ashworth Scale (MAS), biomechanic viscosity, and the reflexive electromyography threshold (RET) of the biceps brachii were used to evaluate the degree of hypertonia.

Results: The statistical analyses of the MAS score, biomechanic viscosity, and RET revealed a significant decrease in spasticity after the injection (all $P<.05$). Moreover, our quantitative parameters (biomechanic viscosity, RET) revealed small changes in spasticity after the BTX-A injection that could not be observed from clinical MAS evaluations. Five of 8 subjects showed a maximal reduction in spasticity (in terms of biomechanic viscosity value) within 6 weeks after the injection, whereas it was notable that all subjects exhibited peak RET values at either 2 or 6 weeks after the injection with variable degrees of relapse of spasticity.

Conclusions: Early relapse of spasticity (within 9 weeks of the injection) can be detected from biomechanic and neurophysiologic assessments in a clinical setup. These quantitative indices provide valuable information for clinicians when making decisions to perform additional rehabilitation interventions or another BTX-A injection in the early stages of treatment.

Key Words: Botulinum toxin type A; Muscle spasticity; Rehabilitation.

MUSCLE SPASTICITY OF LIMBS is a common impairment in patients suffering from cerebrovascular accidents (CVAs). Restricted joint range and pain from spastic hypertonia can cause functional limitations in the activities of daily living and ambulation.[1-3] Within the past decade, the injection of botulinum toxin type A (BTX-A) has been widely used in clinics to focally reduce the spasticity of limbs and is effective in improving the joint range of motion, muscle strength, and motor function.[4-6] It is known that BTX-A can block acetylcholine release from motoneurons and lead to reversible paralysis of the injected muscle area,[7] with its effectiveness being maintained for 2 to 4 months.[8,9] Recent animal studies[10,11] have shown that neurotransmission can be gradually restored by the sprouting of nerves or by functional rehabilitation of intoxicated motor nerve terminals after the injection of BTX-A. Thus, time course observations of the effects of BTX-A injection on spastic muscle, which could provide information about the optimum timing for rehabilitation intervention or reinjection of BTX-A, are crucial for clinical practice.

Conventional clinical assessments may lack objective analysis methods for quantifying the changes in spasticity over time after the injection of BTX-A. The most widely used approach for assessing spasticity is the score-based Modified Ashworth Scale (MAS).[12] However, the MAS is semiquantitative[13] and largely relies on the experience of the examiner. With the unremarkable interrater reliability,[14-16] accurate comparisons might only be made between measurements made by the same trained examiner over a short period of time. When aiming to compare the changes in spasticity after a BTX-A injection, these limitations become major shortcomings when the observation period is lengthened and different examiners are involved.

The velocity-dependent increase in muscle resistance and the hyperexcitability of stretch reflexes are defining features of spasticity.[17,18] Biomechanic studies[19-21] of reactive torque in spastic limbs have furthered our understanding of the velocity-dependent nature of spasticity. Neurophysiologic methods such as electromyography recording and muscle reflexes elicited by electric stimulation[22] provide information on the excessive excitability of stretch reflexes in spastic muscles. The length-related property of spasticity has been defined as the decrease

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Table 1: Summary of the Subjects' Clinical Data and Dosage of the Injection of BTX-A Into the Biceps Brachii

Subject (n=8)	Age (y)	Sex	Months Postinjury	Affected Side	Brunnstrom Stage	Dosage (U)
S1	64	Female	31	Left	V	50
S2	65	Female	24	Left	V	50
S3	50	Female	9	Left	IV	50
S4	61	Male	61	Left	III	100
S5	68	Male	43	Left	III	50
S6	38	Female	14	Right	III	50
S7	70	Male	20	Right	III	50
S8	55	Female	69	Left	IV	50

in the reflexive electromyography threshold (RET) angle in stretched muscles.[23,24] This increased sensitivity to muscle length change is thus effective in showing the excitability of stretch reflexes.[23,24]

We have previously developed a validated approach for quantifying the velocity dependence of muscle resistance in a stretched spastic elbow based on a portable measurement system.[25] This spasticity-assessment device has been extended to measure the threshold angle of the stretch reflex by electromyography recording to allow quantification of the length-related property.[26] In the present study, this integrated portable device was used to record the reactive resistance, joint displacement, and electromyographic signals of spastic elbow joints during manual stretches in a clinical setup, with the aim of quantifying the time course changes in elbow spasticity over a 9-week observation period after the injection of BTX-A.

METHODS

Participants and BTX-A Treatment

All stroke patients were evaluated before participating in the experiments, which were overseen by a qualified physician in the Department of Rehabilitation at Chi-Mei Hospital, Tainan, Taiwan. The inclusion criteria for subjects included (1) flexor spasticity in the affected elbow joint without contracture, (2) the onset of CVA having occurred at least 6 months previously, (3) the presence of stable spasticity, (4) a Brunnstrom stage of at least level 3,[27] and (5) no severe cognitive or affective dysfunction. Subjects provided informed consent for participation in the protocols before undergoing injections and subsequent evaluations, which followed the clinical protocol approved by the local ethics committee. Eight subjects (age range, 38–70y) with previous onsets of CVA (range, 9–69mo) previously completed the 11-week time course observation period. The clinical data of the subjects are summarized in table 1.

Under the guidance of needle electromyography, all subjects were injected with BTX-A (Botox) in the muscles of the forearm and upper arm by the same physician. The dosage and locations of the intramuscular injection were individualized for each patient based on the severity and distribution of the spastic muscles involved. Among the injected muscles, the targeted biceps brachii muscle (one of the main elbow flexors) was always included for injection, at doses ranging from 50 to 100U (see table 1). Other muscles that were injected with intramuscular BTX-A included the flexor digitorum superficialis (50U in 5 subjects), the flexor carpi radialis (50U in 4 subjects), and the flexor carpi ulnaris (50U in 5 subjects). No other medication was prescribed for reducing spasticity during the study, and the rehabilitation program was unchanged during the 11 weeks of observation.

Time Course Evaluation of BTX-A Effects

Spasticity was evaluated at 2 weeks before and 2, 6, and 9 weeks after the injection of BTX-A. All evaluations were conducted by the same physical therapist. The evaluation procedures comprised the clinical MAS, biomechanic measurements, and electromyographic assessments. The clinical assessment was performed by using the MAS with 6 scores (0–5, modified from the original scores of 0, 1, 1+, 2, 3, and 4).[12] In addition, biomechanic and electromyographic data were collected by using a portable measurement system comprising a handheld device and 2 pairs of surface electromyography recording electrodes[a] (fig 1A). The handheld device consists of wrist cuffs with airbags and a lightweight gyroscope. The airbags held on both the ventral and dorsal sides of the wrist are connected to a differential pressure sensor to record the net resistance (pressure). The joint displacement can be obtained from the integration of gyroscopic measurements of the angular rate. As shown in figure 1B, the phase lag between resistance and derived joint displacement can be used for deriving the velocity-dependent property of spasticity. In addition to biomechanic data, electromyography electrodes were placed in parallel to muscle fibers on muscle bellies of the biceps brachii and triceps brachii to measure stretch reflex responses (see fig 1C).

During the data recording, subjects were asked to relax entirely, as monitored by the electromyography recording. The elbow joint was evaluated by manually stretching the forearm in a back-and-forth manner, approximately sinusoidally. Stretching was performed at 4 frequencies (1/3, 1/2, 1, 3/2Hz) with the assistance of a metronome. The consistency of the stretch frequency can be only confirmed from the frequency response of trajectory. The range of elbow flexion and extension was restricted to $-30°$ and $30°$ (where $0°$ indicates a right-angled elbow) by using an elbow limiter (see fig 1A). The reactive resistance, angular rate, and electromyographic signals were digitized simultaneously at a 1000-Hz sampling rate and 12-bit resolution for further processing.

Data Analysis

Our analytic approach first derived the velocity-dependent viscous component from the biomechanic measurements of reactive resistance and joint displacement. We modeled the spastic joint as a second-order system, which the reactive torque contributes from inertia, viscous, and elastic components when sinusoid stretches were imposed.[25] Because the applied force is perpendicular to the forearm, the reactive resistance can be assumed as the reactive torque in following analysis of same subject. Figure 2A shows a representative plot of reactive torque T(t), and joint displacement, X(t), at 1-Hz stretches. The hysteresis loop represents the velocity-dependent damping of the spastic joint model.[16] After representing the displacement X(t) in sinusoid fashion, $A\sin(\omega t)$, in the second-order equation, the averaged complex modulus can be finally derived and defined as $T(t)/X(t+\theta)$, which is the overall magnitude of the vector sum of the real part ($K\text{-}I\omega^2$) and imaginary part ($B\omega$) in figure 2B.[25] By shifting the displacement with the phase lag, $X(t+\theta)$, the averaged complex modulus can be estimated and then used to derive the viscous component ($B\omega$) (see figs 2B, 2C). Figure 2D shows the $B\omega$ estimated at 4 stretching frequencies (ie, 1/3, 1/2, 1, 3/2Hz) denoted as $B\omega_{1/3}$, $B\omega_{1/2}$, $B\omega_1$, and $B\omega_{3/2}$, respectively. From the 4 $B\omega$ (in $N{\cdot}rad{\cdot}m^{-1}$) estimations, 1 viscosity parameter B