Dose-Dependent Response to Intramuscular Botulinum Toxin Type A for Upper-Limb Spasticity in Patients After a Stroke

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Objective: To test the hypothesis that intramuscular (IM) botulinum toxin type A (BTX) reduces excessive muscle tone in a dose-dependent manner in the elbow, wrist, and fingers of patients who experience spasticity after a stroke.

Design: Randomized, double-blind, placebo-controlled, multicenter, 24-week trial.

Setting: Six academic and 13 private US outpatient medical centers.

Participants: Ninety-one patients with a mean age of 60 years (range, 30–79y). Mean time elapsed from ischemic or hemorrhagic stroke to study enrollment was 25.8 months (range, 0.9–226.9mo).

Interventions: Up to 2 treatments of placebo, or 90, 180, or 360U of BTX. Concurrent splinting and physical therapy protocols were permitted, but no changes were allowed during the study.

Main Outcome Measures: Wrist, elbow, and finger flexor tone assessed by the Modified Ashworth Scale, physician and patient global assessments, pain, FIM instrument, and Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).

Results: Muscle tone decreased more with injections of BTX than with placebo in the wrist flexors at weeks 1, 2, 3, 6, and 9 (P ≤ .026); in the elbow flexors at weeks 1, 2, 3, 4, 5, and 9 (P ≤ .033); and in the finger flexors at weeks 1 and 3 (P ≤ .031). A dose-dependent response was generally observed in tone reduction but not in pain, FIM, or SF-36 measures.

Conclusions: IM BTX reduced muscle tone in a dose-dependent manner in the elbow, wrist, and fingers of patients who experience spasticity after a stroke but did not appear to affect global quality of life or disability.

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

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OVER ONE-HALF MILLION Americans have strokes each year, and as a result some patients develop spasticity and severe upper-limb muscle tone. Untreated, excessive muscle tone can result in a net imbalance of force, leading to deformity across the joints. Common patterns of muscle tone dysfunction in the upper limb after a stroke contribute to skin breakdown, malodor, and poor access for bathing and dressing. Spasticity, a “velocity-dependent increase of tonic stretch reflexes with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex” is a condition that results from a number of neurologic disorders such as spinal cord injury, traumatic brain injury, multiple sclerosis, and stroke. Management of spasticity is generally considered essential to prevent deformities, to improve function, and to relieve distressing symptoms, with optimal medical treatment often requiring multiple interventions. Interventions may include physical therapy, oral and intrathecal antispasticity medications, local chemical neurolysis, and surgical interventions such as dorsal rhizotomies, nerve root resections, myotomies, and tenotomies.

Botulinum neurotoxin intramuscular (IM) chemodenervation procedures provide an important therapeutic adjunct in the treatment of focal spasticity. In skeletal muscle, botulinum toxin type A (BTX) acts by preventing the release of acetylcholine from the presynaptic axon of the motor endplate and by blocking signal transmission at the neuromuscular junction. The effect is a local chemodenervation initially reversed when the preterminal neurite sprouts and reenervates the muscle. Regression of the neurite sprouts and resumption of excytosis from previously BTX-intoxicated nerve terminals subsequently returns the neuromuscular junction to its original state.

Recent studies performed using BTX have shown a dose-related decrease in muscle tone with increased joint mobility after injections into the affected limb. Several open-label and double-blind placebo controlled trials have reported improvement in patients with severe spasticity after BTX injections. Recently, a multicenter study showed that a single set of IM BTX injections reduced wrist and finger muscle tone and associated disability in patients with stroke. The objective of our study was to test the hypothesis that treatment with IM BTX reduces excessive muscle tone in a dose-dependent manner in the wrist, fingers, and elbows of patients who experience spasticity after a stroke.

METHODS

Study Population

Patients were 21 to 80 years of age and weighed at least 60kg. Inclusion criteria consisted of (1) a stroke diagnosed by a neurologist, (2) occurrence of a stroke at least 6 weeks prior to study enrollment, (3) focal spasticity of an upper limb shown by excessive wrist flexor muscle tone score of 3 or higher (very severe) and elbow flexor tone score of 2 or more (severe) as
measured by the Modified Ashworth Scale (MAS; table 1), and (4) ability to give informed consent and comply with study instructions. Exclusion criteria consisted of (1) fixed contracture or profound atrophy in the affected limb; (2) previous or current treatment with any botulinum toxin serotype, phenol, or surgery; (3) current plaster casting for spasticity of the study limb; (4) current treatment with agents that affect neuromuscular transmission; (5) pulmonary function testing (forced expiratory volume at 1 second [FEV1], forced vital capacity [FVC]) less than 65% of predicted value; (6) participation in another clinical trial within 30 days of study entry; (7) diagnosis of myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other condition that might interfere with the study; and (8) known sensitivity to any components of study medication (Clostridium botulinum toxin type A, albumin [human], sodium chloride). Women were excluded if pregnant, breastfeeding, or planning pregnancy during the course of the study.

Participants and investigators could elect to discontinue the study for any reason. Investigators could discontinue participants for administrative reasons such as noncompliance or failure to meet visit schedule or for reasons related to treatment. The study was conducted at 19 outpatient clinics, 6 of which were associated with university centers, whereas the remaining were private. Some of the clinics were associated with large medical centers. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices and was approved by the governing institutional review board at each study center. All patients provided written informed consent.

### Study Design and Procedures

#### Overall study design.

The overall purpose of this study was to evaluate the safety and efficacy of 2 treatment cycles of IM injections of BTX in patients with focal upper-limb spasticity after a stroke. Scheduled patient assessments occurred at weekly intervals for the first 6 weeks of the study and then at weeks 9, 12, 18, and 24. The overall study flow is shown in figure 1. Patients were randomized to receive 1 of several doses of BTX treatment or placebo via a computer-generated randomization code. There was no crossover aspect in the study design and implementation.

Demographic and medical data, measures of muscle tone, functional disability, pain, and quality of life (QOL) were obtained at the baseline visit. Ashworth scores, global assessments, functional disability, and pain scores were measured every week for the first 6 weeks and then after 9, 12, 18, and 24 weeks in the study. Measures of functional disability and QOL (FIM instrument, Medical Outcomes Study 36-Item Short-Form Health Survey [SF-36]) were assessed at week 6 and at every subsequent visit, except the SF-36, which was not assessed at week 9.

#### Procedures

After obtaining written consent, patients were evaluated for study eligibility, and baseline values were obtained at the first visit. Subjects were randomized to receive IM injections of placebo or 90, 180, or 360U of BTX. Placebo and the study drug were identical in appearance, and both were prepared by a pharmacist not directly involved in the study to conceal the identity of interventions to investigators and participants. Each vial of BTX (Botox) contained 100U of BTX with 0.5mg of human serum albumin and 0.9mg of sodium chloride in a sterile, vacuum dried form without preservatives. Each vial of placebo contained 0.5mg of serum albumin and 0.9mg of sodium chloride. Each 100U vial was diluted with 0.9% sterile,

### Table 1: Modified Ashworth Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No increase in muscle tone</td>
</tr>
<tr>
<td>1</td>
<td>Slight increase in muscle tone, manifested by a catch and release or by minimal resistance through remainder (less than half) of the range of motion (ROM) when the limb is moved in flexion or extension</td>
</tr>
<tr>
<td>2</td>
<td>More marked increase in muscle tone through most of the ROM, but affected limb is easily moved</td>
</tr>
<tr>
<td>3</td>
<td>Considerable increase in muscle tone; passive movement difficult</td>
</tr>
<tr>
<td>4</td>
<td>Limb rigid in flexion or extension</td>
</tr>
</tbody>
</table>

NOTE. Half-point increments allowed.

Fig 1. Participant flow, interventions, and efficacy measurements. *Efficacy measures after the first treatment cycle included: MAS scores (wrist, elbow, fingers), physician and patient global assessments, pain assessment, FIM, and SF-36. †Efficacy measures after the second treatment cycle included: MAS scores (wrist) and global assessments.
preservative-free saline. To mask the study drug, the injection volume was kept the same for all doses of BTX. The total injection volume (study drug and placebo) was adjusted to 4mL by adding additional saline.

There were no specific physical therapies or splinting protocols performed within the study. However, the investigators could implement concurrent therapies except during the first week after injection, when no changes in the use of therapeutic or stabilization devices (eg, splints, casts, orthotic devices) were permitted. Use of antispasticity medications during the study was not restricted. The investigators were permitted to add, change the dose, or stop antispasticity medication at their discretion.

Injected muscles. Muscles chosen for injection were based on previous experience with BTX in upper-limb spasticity. They consisted of the flexor carpi ulnaris, flexor carpi radialis, biceps brachii, flexor digitorum profundus, and the flexor digitorum sublimis (table 2). The second treatment cycle, if given, was identical to the first in dose and location of injections. All injections were given under electromyographic guidance.

Eligibility for a second intervention. Subjects were eligible for a second treatment cycle 12 weeks or more after the first only if they showed MAS scores of 2 or higher at the wrist and/or elbow flexor muscles and pulmonary function measurements did not decrease by more than 15% from baseline. Therefore, subjects were eligible to receive a second intervention 12 weeks after entering the study. Patients received the same blinded treatment at both injection cycles.

Efficacy and Safety Measures

The primary efficacy variable was wrist flexor tone as measured by a 9-point MAS (0, no increase in muscle tone; 4, limb rigid in flexion or extension, with half point increments allowed; table 1). The Ashworth Scale, originally developed in 1964, has been the conventional measure of spasticity used both clinically and in research studies with good intra- and interrater reliability when used by trained medical professionals. To provide finer steps in grading spasticity, a 9-point scale was previously developed by Allergan Inc with 0.5-grade intervals. In a pilot, health care provider, questionnaire study (unpublished study, 1997), a direct comparison of the standard (integer) and expanded (0.5-grade step) Ashworth scales for evaluating upper-limb spasticity in a poststroke patient population found a significant correlation (P=0.0001) between the standard and expanded scales, and among raters (Allergan, unpublished internal study 191622-007, 1997).

Secondary measures of efficacy included elbow and finger flexor tone (also measured by a 9-point MAS), a 9-point physician global assessment and patient global assessment of response to treatment (−4, very marked worsening; 0, unchanged; 4, very marked improvement), a 5-point frequency of pain scale (0, never; 4, constant), a 5-point severity of pain scale (0, none; 4, very severe, intolerable), a 5-point assessment of functional disability (0, no functional disability; 4, very severe disability), the 7-point FIM instrument (1, total assistance; 7, complete independence), and the SF-36. The SF-36 is considered to be a reliable, validated, generic instrument used to determine the health-related QOL in diverse patient groups. The SF-36 covers 2 dimensions (physical and mental health) for 8 separate domains: physical functioning, role–physical, bodily pain, general health, vitality, social functioning, role–emotional, and mental health. In addition to the 35 items that make up the 8 domains, an additional item measures health transition. The FIM, considered to be a reliable and valid instrument, is used to determine the degree of disability that patients experience and the progress that they make through programs of medical rehabilitation. The FIM scores 18 functional activities on a 7-level scale containing 2 principal components representing physical and cognitive functioning, respectively.

Clinical efficacy criterion. A decrease of 1 point or more on the MAS for any given subject and/or an absolute 20% difference in the physician’s global assessment score between the treatment groups were also proposed as clinically significant changes. For the purposes of this study, half-point decreases on the MAS were allowed to be recorded. Clinical effectiveness of treatment was defined by evaluating the difference between treatment groups for the mean decrease from baseline of the MAS score. If the difference between the decrease from baseline of the MAS score of 1 group when compared with the decrease from baseline of another group was 0.5 points or greater, this difference was prospectively defined as clinically significant.

Safety. Patients were monitored for adverse events throughout the study. Investigators rated events as mild, moderate, or severe and evaluated for any causal relationship to the study. A serious adverse event was defined as an event that was fatal, life-threatening, permanently disabling, required inpatient hospitalization or prolongation of an existing hospitalization, or was a congenital anomaly, cancer, or an overdose. At study entry, week 2, and study exit, blood and urine samples were collected for routine urine analysis, serum chemistry, and hematology assays. Physical examinations were conducted before the study and at study exit and included measurements of heart rate and blood pressure. Abnormal physical findings were documented. Pulmonary function testing (FEV1, FVC) was performed at study entry, at weeks 1, 6, and 12, and then at every subsequent visit.

Statistical Methods

It was determined a priori that with 15 subjects in each group, the study had 70% power to detect a .75-point difference between treatment groups in the mean MAS scores (primary efficacy variable).

Efficacy. Efficacy data were analyzed for participants who received study medication and completed at least 6 weeks of visits. For the primary efficacy variable (MAS score), the 1-way analysis of covariance (ANCOVA) of ranks was performed, including the main treatment effect and the covar-iant—time since onset of a stroke. For other variables (FIM, SF-36, global assessments, functional disability, pain), the 1-way analysis of variance (ANOVA) of ranks was used. The Kruskal-Wallis 1-way ANOVA of ranks was used to control for multiple comparisons between treatment groups. Group comparisons (Wilcoxon rank-sum test) were evaluated only if the overall differences were significant (P<.05). Nonordinal

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**Table 2: BTX Dose Regimen**

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Low-Dose Group</th>
<th>Middle-Dose Group</th>
<th>High-Dose Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biceps brachii</td>
<td>0U</td>
<td>50U</td>
<td>100U</td>
</tr>
<tr>
<td>Flexor carpi radialis</td>
<td>0U</td>
<td>15U</td>
<td>30U</td>
</tr>
<tr>
<td>Flexor carpi ulnaris</td>
<td>0U</td>
<td>10U</td>
<td>40U</td>
</tr>
<tr>
<td>Flexor digitorum profundus</td>
<td>0U</td>
<td>7.5U</td>
<td>15U</td>
</tr>
<tr>
<td>Flexor digitorum sublimus</td>
<td>0U</td>
<td>7.5U</td>
<td>15U</td>
</tr>
</tbody>
</table>

*The volume injected and number of injection sites remained constant among the groups.*
data were analyzed with the Pearson chi-square or the Fisher exact test.

**Adverse events.** Adverse event incidence was calculated from the number of subjects exposed to the study drug. The incidence of adverse events was evaluated by using a Fisher exact test. All tests were 2 sided, and a P value of less than .05 was considered significant.

## RESULTS

### Study Population

Nineteen centers enrolled 91 participants (61 men, 30 women; mean age, 60.9; range, 30.4–79.4). Demographic characteristics are summarized in table 3. The mean time elapsed from stroke to study enrollment was 25.8 months (range, 0.9–226.9mo).

There was a significant difference among treatment groups for the type of stroke (P = .026), with more thrombotic strokes in the 90U (12/21, 57.1%), 360U (17/21, 81.0%), and placebo groups (15/26, 57.7%) than in the 180U group (7/23, 30.4%). The remaining types of strokes across all treatment groups were embolic (16/91, 17.6%), hemorrhagic (19/91, 20.9%), or of unknown etiology (5/91, 5.5%).

A total of 11 patients (52.4%) in the 90U group and 13 (56.5%), 15 (71.4%), and 15 (57.7%) in the 180U, 360U, and placebo groups, respectively, had strokes in the right hemisphere. One patient (4.8%) in each of the 90 and 360U groups had a stroke in the brainstem.

A total of 25 of 91 patients (27.5%) were using antispasticity medication at baseline; the rest (72.5%) were not. There were no significant differences detected between treatment groups when examining for the presence or absence of antispasticity medications.

### Randomization

The participant flow, numbers, timing of randomization assignment, study interventions, and measurements for each randomized group are shown in figure 1. Of the 91 subjects, 65 (71.4%) were randomized to receive BTX (21 to a low-dose group, 23 to a middle-dose group, 21 to a high-dose group) and 26 (28.6%) were randomized to receive placebo. Seventy-seven of 91 subjects (84.6%) completed the study, whereas 14 subjects (10 BTX, 4 placebo) were discontinued before completion (13 for administrative reasons, ie, missed visits; 1 subject, treated with placebo, withdrew because of lack of efficacy). There were 67 subjects (73.6%) who received a second treatment cycle in this study: 16 subjects received a low (90U) dose, 15 subjects received a middle (180U) dose, 18 subjects received a high (360U) dose, and 18 subjects received the placebo. A majority of the subjects (57.1%) received the second treatment at week 12.

### Primary Efficacy Results After First Intervention

#### Wrist flexor MAS scores.

At baseline, there were no differences detected between groups in wrist flexor tone. After injection, there was a general trend in reduction of wrist flexor tone during the first 9 weeks after injection with BTX but not placebo. Summary results of the primary measure of efficacy are shown in figure 2. Subjects who received the highest BTX dose (360U) consistently showed more reduction in excessive wrist tone (vs subjects who received the placebo) at all of the visits through week 12. Significant mean reductions ± standard deviation (SD) in wrist flexor tone were shown in the high-dose group compared with placebo at weeks 1 (−1.2 ± 0.8 vs −0.4 ± 0.7; P = .001), 2 (−1.7 ± 0.8 vs −0.7 ± 0.8; P = .001), 3 (−1.5 ± 0.9 vs −0.6 ± 0.6; P = .001), 6 (−1.6 ± 0.9 vs −0.7 ± 0.7; P = .001), and 9 (−1.4 ± 0.9 vs −0.6 ± 0.7; P = .005) (ANCOVA).

Significant mean reductions in the wrist flexor tone were shown in the 180U group compared with placebo at weeks 1 (−0.7 ± 0.9; P = .046), 3 (−1.0 ± 1.1; P = .024), and 6 (−1.0 ± 1.1; P = .038) and for the 90U group at weeks 1 (−0.9 ± 0.7; P = .026), 3 (−1.3 ± 0.9; P = .001), 6 (−1.2 ± 0.6; P = .023), and 9 (−1.2 ± 0.9; P = .034) (ANCOVA).

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### Table 3: Subject Demographics

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Placebo (n=26)</th>
<th>Low Dose (90U) (n=21)</th>
<th>Middle Dose (180U) (n=23)</th>
<th>High Dose (360U) (n=21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>60.6</td>
<td>59.3</td>
<td>61.1</td>
<td>59.0</td>
<td>NS</td>
</tr>
<tr>
<td>Range</td>
<td>33.8–76.0</td>
<td>30.4–76.1</td>
<td>39.6–79.4</td>
<td>35.4–77.7</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Men</td>
<td>13</td>
<td>16</td>
<td>15</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>13</td>
<td>5</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean ± SD</td>
<td>76.0±14.2</td>
<td>79.5±15.4</td>
<td>75.4±13.6</td>
<td>83.7±22.1</td>
</tr>
<tr>
<td>Months after a stroke</td>
<td>Mean (Range)</td>
<td>26.6 (2.1–211.7)</td>
<td>28.7 (0.9–108.5)</td>
<td>31.2 (1.2–226.9)</td>
<td>16.5 (2.6–99.2)</td>
</tr>
</tbody>
</table>

NOTE. Not significant (NS) at P ≤ .05.
Together, these data indicate that BTX injections improved muscle tone at the wrist in a dose-dependent manner in patients who had had a stroke. The group given the highest dose (360U) showed the greatest response in the main outcome measure compared with placebo at all visits.

**Secondary Efficacy Results After First Intervention**

**Elbow MAS scores.** Subjects who received the 2 highest BTX doses (360, 180U) showed more reduction in excessive muscle tone at the elbow compared with subjects injected with a placebo at all visits up to week 9 (fig 3).

Significant mean reductions ± SD in the elbow flexor tone were shown in the 180U group compared with placebo at weeks 1 (−1.0±1.2 vs −0.4±0.6; P=.001), 2 (−1.0±1.2 vs −0.4±0.6; P=.003), 3 (−0.9±1.3 vs −0.2±0.6; P=.006), 4 (−1.0±1.2 vs −0.4±0.5; P=.006), 5 (−1.0±1.0 vs −0.4±0.6; P=.005), and 9 (−0.6±1.2 vs −0.2±0.4; P=.029) (ANCOVA).

Significant mean reductions in the elbow flexor tone were shown in the 360U group compared with placebo at weeks 1 (−0.9±0.8; P=.001), 2 (−1.1±0.7; P=.001), 3 (−1.0±0.7; P=.001), 4 (−0.9±0.7; P=.026), 5 (−0.8±0.6; P=.045), and 9 (−0.7±0.6; P=.004) (ANCOVA).

**Finger flexor MAS scores.** Reduction in excessive muscle tone in the finger flexors after BTX injections was not as robust as the response observed in the wrist or elbow. Subjects who received the 2 highest BTX doses (180, 360U) in the finger flexor muscles improved significantly more than those subjects injected with a placebo at week 1 (0.8±0.9; P=.020; −0.9±0.7, P<.009 vs −0.3±0.8, respectively). Only scores in the 360U group improved more than the placebo group at week 3 (−1.1±0.7 vs −0.4±0.7; P=.003) (ANOVA).

**Global assessment of response to treatment.** There were no detectable global responses to low-dose (90U) BTX treatment. Patients in the 360U BTX group had mean scores ± SD of 1.5±0.9, 1.9±1.0, 1.7±1.0, and 1.7±1.1 points at weeks 1, 2, 3, and 5, respectively, compared with placebo mean scores of 0.7±0.8, 0.7±0.8, 0.8±0.8, and 0.7±0.8 (P=0.001) (ANOVA). The 180U BTX group had mean scores of 1.3±0.9, 1.5±0.9, 1.4±1.0, and 1.4±0.8 points on this scale at 1, 2, 3, and 5 weeks postinjection, respectively, versus placebo (P=.013) (ANOVA). A dose-dependent response to treatment was not evident in patients’ global assessments (data not shown).

**Functional disability assessments.** No significant differences in functional disability were detected between treatment groups. Baseline functional disability scores rated by participants ranged from 2.7 in the 180U group to 3.0 (severe disability, normal activities limited) in the placebo group. Baseline functional disability scores rated by investigators ranged from 2.6 in the 90U group to 3.0 in the placebo group.

**Pain assessments.** No significant differences in the frequency or intensity of pain were detected among treatment groups. Only 27% (25/91) of subjects indicated that they had pain at baseline. Mean pain frequency scores at baseline were low and ranged from 1.0 (pain occurs sometimes) in the placebo and 90U groups to 1.3 in the 2 highest (180, 360U) dose groups. Mean pain intensity scores at baseline ranged from 1.3 (mild pain) in the 90U group to 1.5 in the 2 highest dose groups.

**Measures of function.** No significant differences in composite FIM scores were detected between treatment groups. Statistically significant differences were observed in individual domains at certain visits, but a dose-response relationship between FIM scores and BTX treatment was not observed.

**Quality of life.** On the SF-36, the only significant improvement compared with placebo was shown by patients in the 90U BTX group at week 6 on the social functioning section (mean ± SD, 20.8±34.0 vs −10.0±24.2; P=.002), in which an improvement is indicated as an increase on the scale (ANOVA). A dose-dependent relationship between SF-36 scores and BTX administration was not observed. There was also a difference (P=.014) between the groups on the social functioning section at week 6. The mean change from baseline for all of the groups was as follows: placebo (−10.0±24.2), 90U (20.8±34.0), 180U (−5.1±42.7), and 360U (−4.4±27.9) (ANOVA).

**Results of Efficacy Measures After a Second Intervention**

Compared with results of the first set of injections with BTX, a strong dose-response relationship was not observed after the second set of injections. Data after the second treatment (given at week 12) were only collected for wrist muscle tone and a physician global assessment. No differences were seen in either measure among treatment groups. However, differences were observed when these data were analyzed according to the number of patients who responded with clinical success (defined as a 1-point reduction in the wrist MAS score). At week 18, 14 of 16 patients in the high-dose (360U) group were responders, compared with 6 of 17 patients in the placebo group (P=.004). This response was maintained at 12 weeks after the second injection (week 24), when 11 of 14 patients in the high-dose group sustained muscle tone reduction by at least 1 point in the wrist compared with 5 of 13 patients treated with placebo (P=.054).

**Safety Analysis**

Adverse events, regardless of causality, occurred in 83.1% (54/65) of the patients treated with BTX and 65.4% (17/26) of the patients treated with placebo. Serious adverse events were
reported in 15 patients during the study, but none were considered treatment-related by study investigators (table 4). Adverse events that were reported in a least 10% of subjects (in any group) included decreased lung function, respiratory infection, peripheral edema, arthralgia, arm pain, hypertension, depression, and abdominal pain. There were 9 treatment-related adverse events reported for 5 patients treated with BTX, and none were reported for patients who received placebo. Most of these events were considered mild or moderate in severity. However, 2 events, arm pain and hemotoma at the injection site that occurred in the 90U group, were considered severe. Both events were self-limiting, and neither event required discontinuation from the study.

No differences were detected between groups for respiratory-related adverse events or for FVC measures (data not shown). Similarly, no differences in FEV1 data were detected between treatment groups at baseline, or in change from baseline through week 12 (single treatment exposure); however, at week 18, there was a greater reduction in the FEV1 for the high-dose (360U) group than for the other 3 groups (P < .005). Two independent pulmonologists reviewed the data and deemed that this change was not clinically significant because the maximal mean change was only 220mL, a change representing less than 10% of the average baseline measure. Week 18 data were also confounded in that they included 2 subsets of subjects; some that received only 1 injection set at day 0 and others that received a second injection set at week 12.

**DISCUSSION**

The main findings from our multicenter study of patients who received 2 sets of IM injections of BTX for excessive upper-limb muscle tone after a stroke are as follows. First, IM BTX reduced excessive muscle tone in the elbow, wrist, and fingers. Second, the tone-reducing effects of BTX were dose dependent. And third, sustained benefit occurred when injections were repeated after 12 weeks.

Our findings are consistent with an earlier multicenter study23 that showed a single set of BTX injections reduced muscle tone in the wrist and fingers. Although excessive muscle tone improved in the upper limb after BTX injections in our subjects, we did not detect functional benefit, nor did we observe improvement in the QOL. The results also show a placebo effect at some of the time points assessed, a well-known phenomenon in this patient population. An important distinction between our findings and those reported earlier by Brashear et al23 was that, in the previous study, improvement was seen in a 4-point disability scale after a single set of BTX injections. One explanation for differences in functional outcomes between the 2 studies may be that, in the present study, functional measures might not have captured small but important changes in the upper limb resulting from BTX injections. For example, the Disability Assessment Scale (reported by Brashear,23 but not used in the present study) measured hygiene and the effect of hygiene-related disabilty on other areas, whereas the FIM (measured in the present study) does not provide for such detailed assessment of hygiene. Further research will be needed to determine what category of upper-limb hygiene (eg, cleanliness of the palm, pain, ulceration) improves after BTX injections in patients who experience spasticity after a stroke.

Another possibility might explain differences in functional outcomes observed between the present and an earlier study23 of BTX for the treatment of upper-limb spasticity after a stroke. We injected different doses of BTX compared with doses previously reported. In our study, subjects in the high-dose group received 160U in the wrist and finger flexors, with the remaining 200U given into the elbow flexors. In contrast, the previous investigators23 injected a mean dose of 221U into the wrist and finger flexors, but no injections were given into the elbow flexors. Thus, compared with our study, subjects reported by Brashear23 received higher doses of BTX into the wrist and finger flexors and, as a result, might have gained substantially greater functional benefit.

In the present study, we showed that repeated BTX injections sustained muscle tone reduction, whereas only 1 set of BTX injections were previously studied in a blinded manner. However, in an open-label extension of findings reported by Brashear,23 subjects benefited from a subsequent set of injections 12 weeks later. This 12-week duration of BTX effect on muscle tone is consistent with previous experimental33 and clinical34-37 observations. Together, these findings indicate that repeated injections of BTX are likely to result in continued clinical benefit.

BTX treatment appeared to reduce excess muscle tone in the elbow and finger muscles of our stroke subjects, but the effect measured in the wrist appeared more robust. However, our entry criteria required an MAS score of 3 or more at the wrist, compared with a score of only 2 or more at the elbow. Further, no entry criteria were required for finger flexor tone. Thus, there was more room for improvement in wrist muscle tone compared with tone at the elbow or fingers. In addition, only 1 of the 3 elbow flexors (biceps brachii) was injected with BTX, and doses used for finger flexor muscles might have been too low for a noteworthy response. (A reduction in excessive wrist muscle tone by at least 1 Ashworth grade was considered clinically meaningful.) A previous study showed improvement in muscle tone after injections of 50U of BTX in the finger flexor muscles,35 whereas in our study, the highest BTX dose injected into the finger flexors was 30U. Together these factors may explain why we observed greater tone reduction at the wrist compared with responses measured in the fingers or elbows.

One of the limitations of this study was that no evaluation or entry restriction was applied to patients who may have had underlying paresis. In such patients, a reduction of spastic tone would not be associated with any functional improvement. We were attempting to use a scale that measures broad aspects of function to evaluate a focal treatment in a population of patients who may not have had underlying motoractive function capability. Also, attempts were made to evaluate function by using a broad scale that is not specific to measure the effect of a focal muscle treatment that is likely to affect passive function to a greater degree than active function, especially in a group of patients with underlying compromised active function not related to the spasticity. It is therefore not known what, if any, effect underlying paresis may have had on functional improvement.

Repeated BTX injections at doses up to 360U were safe and well tolerated in our subjects. Although it is possible that different dilutions of BTX may have affected the results after injection, animal studies33,38 indicate that location of injection relative to the motor endplate and dose are the most important determinants of outcome. Therefore, it seems unlikely that differing dilutions of BTX used in our study affected the results.

There were no treatment-related serious adverse events reported. Nonetheless, these data must be interpreted cautiously because study investigators determined the treatment-related adverse events, a potential source of bias. Furthermore, FEV1 was decreased in some patients given the highest (360U) dose, but the changes observed were not considered clinically meaningful. Further research is needed to evaluate critically the safety of BTX therapy in patients with diminished respiratory function.
CONCLUSIONS

Data reported here support the hypothesis that IM BTX reduces excessive muscle tone in a dose-dependent manner in the elbow, wrist, and fingers of patients who experience spasticity after a stroke.

Acknowledgments: The BOTOX 133/134 Post-Stroke Spasticity Group includes: Cynthia Comella, MD (Rush-Presbyterian-St. Luke’s Medical Center, Chicago, IL); Movement and Mobility Center, Des Plaines, IL); Mary Dombovy, MD (St. Mary’s Hospital, Rochester, NY); Gerard Francisco, MD (Kessler Institute for Rehabilitation, East Orange, NJ); Alvin Glass, MD (Kaiser Rehabilitation, Vallejo, CA); Richard Lazar, MD (Schwab Rehabilitation Hospital & Care Network, Chicago, IL); Erwin Montgomery, MD (University of Arizona, Tucson, AZ); Susan Pierson, MD (Braintree Hospital, Braintree, MA); David Simpson, MD (Mt. Sinai Medical Center, New York, NY); Joel Stein, MD (Spaulding Rehabilitation Hospital, Boston, MA); Joseph Stillo, MD (Bettacharach Hospital, Pomona, NJ); Daniel Tarsy, MD (Beth Israel Deaconess Medical Center, Boston, MA); David Villasana, MD (North Atlanta Neurological Associates, Marietta, GA); and Richard Zorzowitz, MD (University of Pennsylvania Medical Center, Philadelphia, PA).

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Supplier