

INTRAMUSCULAR INJECTION OF BOTULINUM TOXIN FOR THE TREATMENT OF WRIST AND FINGER SPASTICITY AFTER A STROKE

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ABSTRACT

Background Spasticity is a disabling complication of stroke, and it is uncertain whether intramuscular injections of botulinum toxin type A reduce disability in persons with spasticity of the wrist and fingers after a stroke.

Methods We performed a randomized, double-blind, placebo-controlled, multicenter trial to assess the efficacy and safety of one-time injections of botulinum toxin A (200 to 240 units) in 126 subjects with increased flexor tone in the wrist and fingers after a stroke. The primary outcome measure was self-reported disability in four areas: personal hygiene, dressing, pain, and limb position (on a four-point scale ranging from no disability to severe disability) at six weeks; at base line, each subject selected one of these areas in which there was moderate-to-severe disability as the principal target of treatment.

Results Subjects who received botulinum toxin A had greater improvement in flexor tone in the wrist and fingers at all follow-up visits through 12 weeks than did subjects who received placebo ($P < 0.001$ for all comparisons). Subjects treated with botulinum toxin A had greater improvement in the principal target of treatment at weeks 4, 6, 8, and 12 ($P < 0.001$, $P = 0.03$, and $P = 0.02$, respectively); at week 6, 40 of the 64 subjects in the botulinum-toxin group (62 percent), as compared with 17 of the 62 in the placebo group (27 percent), reported improvement of at least one point on the Disability Assessment Scale in the principal target of treatment ($P < 0.001$). There were no major adverse events associated with injection of botulinum toxin A.

Conclusions Intramuscular injections of botulinum toxin A reduce spasticity of the wrist and finger muscles and associated disability in patients who have had a stroke. (N Engl J Med 2002;347:395-400.)

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EVERY year, almost 750,000 persons have strokes in the United States, and many are left with disabling spasticity.^{1,2} Spasticity in the hands and wrists is especially disruptive because it can interfere with dressing, washing, and other activities of daily living.²

Although a number of studies have demonstrated that botulinum toxin type A decreases muscle tone in spastic muscles,³⁻⁸ only one small, controlled study has

shown functional improvement in the use of a limb with this therapy.⁹ Nonetheless, it is common practice to treat focal spasticity after a stroke with injections of botulinum toxin A. We conducted a multicenter, double-blind, placebo-controlled trial to assess the effects of one set of injections with botulinum toxin A on measures of disability with respect to self-care, limb position, and pain, as well as on muscle tone.

METHODS

Study Population

The study began on April 30, 1999, and ended on February 29, 2000. Subjects were eligible for the study if they were at least 21 years old, had had a stroke at least six months earlier, and had focal spasticity of the wrist and fingers, as demonstrated by a score of 3 or 4 for wrist flexor tone and a score of 2 or higher for finger flexor tone on the Ashworth Scale, with 0 indicating normal muscle tone, and 4 rigid flexion.¹⁰ An additional criterion for enrollment was evidence of difficulty in maintaining hygiene or dressing, pain, or malposition of the wrist or fingers, as evidenced by a score of 2 or 3 on the Disability Assessment Scale, with 0 indicating no disability, and 3 severe disability.

Exclusion criteria were a fixed contracture or profound muscle atrophy in the spastic limb; prior or planned treatment of the limb with any botulinum toxin serotype or with phenol, alcohol, or surgery; a change in oral medication for spasticity in the previous three months; treatment with intrathecal baclofen; or treatment with agents affecting neuromuscular transmission. Women were excluded if they were pregnant, lactating, or planning to become pregnant during the course of the study.

The study was approved by the institutional review board at each participating center. All subjects provided written informed consent.

Study Design

The study was a multicenter, double-blind, randomized comparison of one set of intramuscular injections of botulinum toxin A with one set of injections of placebo. Subjects were randomly assigned to receive a total dose of 200 to 240 units of botulinum toxin A (Botox, commercial lot 2024, Allergan) or placebo (botulinum

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toxin A vehicle): 50 units injected in each of four wrist and finger muscles (50 units per muscle), with optional injections in one or two thumb muscles (20 units per muscle). The doses of botulinum toxin A were similar to those used in previous trials.^{11,12} The placebo and active drug were identical in packaging and appearance.

The study protocol was developed jointly by Dr. Brashear and the sponsor as a phase 3 study. The sponsor was responsible for data management and statistical analysis. The interpretation of the data and preparation of the manuscript were performed by all the authors, who had full access to the data. The content of the manuscript and the decision to submit it for publication were not controlled by the sponsor.

Outcome Measures

Functional Disability

At base line and at weeks 1, 4, 6, 8, and 12, functional disability was rated with the use of the four-point Disability Assessment Scale; the score at week 6 was the primary end point. At all visits, functional disability caused by spasticity of the fingers or wrist was assessed by study investigators who were unaware of the treatment assignments. Four areas of disability were assessed: hygiene (defined as the extent of palm maceration, ulceration, or infection; cleanliness of the palm, ease of cleaning, and nail trimming; and the effect of hygiene-related disability on other areas of functioning), dressing (the ability to dress and the effect of dressing-related disability on other areas of functioning), limb position (psychological or social interference associated with spasticity), and pain (intensity and interference with activities of daily living). A previous study has demonstrated good interrater and intrarater reliability for the Ashworth Scale and the Disability Assessment Scale, as well as a good correlation between the scores on the two scales.¹³ At base line, each subject (or the subject's caregiver), together with a study investigator, selected one of the four areas of disability as the principal target of treatment. The target was an area in which disability was rated as moderate or severe.

Muscle Tone

The tone of the wrist and finger flexors was evaluated by study investigators at all follow-up visits with the use of the five-point Ashworth Scale.¹⁰ On the basis of the findings of a previous study, a response to treatment was defined as at least a one-point improvement from base line in scores for muscle tone in the wrist and fingers.¹⁴

Global Assessment

At each follow-up visit, the overall response to treatment was evaluated by the study investigators and by the subjects or caregivers with the use of the Global Assessment Scale (with a score of -4 indicating very marked worsening, 0 no change, and +4 very marked improvement).¹⁵ The scores were compared with the pretreatment status; there were no base-line measurements.

Safety

Adverse events were assessed by the study investigators at each follow-up visit. A serious adverse event was defined as an event that was fatal, life-threatening, or permanently disabling or that required or prolonged hospitalization. Vital signs were assessed at every visit, and standard laboratory tests were performed before the administration of the study drug and on the day of the last visit.

Measurement of Neutralizing Antibodies

Blood specimens obtained before and after treatment were analyzed for neutralizing antibodies to botulinum toxin A with the use of the mouse protection assay.¹⁶ These analyses were conducted by an independent laboratory (Biological Test Center, Irvine, Calif.).

Statistical Analysis

We planned to enroll 120 subjects in order to ensure that 50 subjects per group would complete the study. The study had a statistical power of 80 percent to detect a 0.5-point difference between groups in the mean change in scores for muscle tone from base line to six weeks. A difference of 0.5 point in the mean decrease from the base-line score was considered to be clinically significant. We conducted a separate analysis that included only subjects who had at least a 1-point improvement from base line in the muscle-tone score.

Efficacy analyses included all treated subjects who completed the follow-up visits, and safety analyses included all treated subjects. A P value of less than 0.05 was considered to indicate statistical significance. Continuous and ordinal variables were analyzed with the use of the Kolmogorov-Smirnov test and Spearman's rank correlation coefficient. Scores on the Ashworth Scale and the Disability Assessment Scale were analyzed as the change from base line. Two-sided tests were performed and 95 percent confidence intervals calculated for mean scores in each group. Categorical variables and adverse events were analyzed with the use of Fisher's exact test.

RESULTS

Subjects

Of the 126 subjects enrolled in the trial, 122 completed it. All 64 subjects randomly assigned to receive botulinum toxin A completed the trial, as compared with 58 of the 62 subjects randomly assigned to receive placebo. The base-line characteristics of the subjects did not differ significantly between the two groups (Table 1).

Doses and Injections

The mean (\pm SD) dose of botulinum toxin A was 221.3 ± 18.8 units. In all subjects, the study drug was injected into the flexor carpi radialis, the flexor carpi ulnaris, the flexor digitorum profundus, and the flexor digitorum superficialis muscles. Ten subjects also received injections in the flexor pollicis longus muscle (7 of 64 in the botulinum-toxin group and 3 of 62 in the placebo group); 3 subjects, all in the placebo

TABLE 1. BASE-LINE CHARACTERISTICS OF THE SUBJECTS.

CHARACTERISTIC	PLACEBO (N=62)	BOTULINUM TOXIN A (N=64)
Age		
Mean — yr	62	61
Range — yr	23–87	23–88
≥ 60 yr — no. (%)	34 (55)	34 (53)
Female sex — no. (%)	27 (44)	36 (56)
Mean height — cm	170.8	168.0
Mean weight — kg	78.3	76.5
Race or ethnic group — no. (%)		
White	46 (74)	53 (83)
Black	14 (23)	7 (11)
Hispanic	1 (2)	3 (5)
Asian	1 (2)	0
Other	0	1 (2)
Mean duration of spasticity — yr	4.9	4.6

group, received injections in the adductor pollicis muscle; and 63 subjects received injections in both thumb muscles (30 in the botulinum-toxin group and 33 in the placebo group).

Efficacy

The choice of the principal target of treatment at base line indicated that subjects were more concerned about dressing, limb position, and hygiene than they were about pain. Of the 64 subjects in the botulinum-toxin group and the 64 in the placebo group, 21 and 19 selected dressing as the principal target, 17 and 16 selected hygiene, 16 and 22 selected limb position, and 10 and 5 selected pain, respectively.

Subjects treated with botulinum toxin A had greater improvement in the principal target of treatment than did subjects who received placebo. At six weeks, 40 subjects in the botulinum-toxin group (62 percent), as compared with 17 in the placebo group (27

percent), had improvement in the principal target of treatment ($P < 0.001$). In addition, subjects in the botulinum-toxin group had significantly greater improvement at weeks 4, 8, and 12 ($P < 0.001$, $P = 0.03$, and $P = 0.02$, respectively). The results at weeks 6 and 12 are shown in Table 2.

We also evaluated the effects of botulinum toxin A on all areas of functional disability, regardless of whether or not they were selected as the principal target of treatment. Six weeks after the injections were administered, 53 of the 64 subjects treated with botulinum toxin A (83 percent) had at least a one-point improvement in the score on the Disability Assessment Scale in one or more of these areas, as compared with 33 of the 62 subjects who received placebo (53 percent) ($P = 0.007$).

Subjects who received botulinum toxin A had greater improvement in mean scores for flexor tone in the wrist and fingers at all follow-up visits than did sub-

TABLE 2. CHANGES IN MEAN SCORES FOR THE EFFICACY VARIABLES.

VARIABLE	SCORE (95% CI)*		P VALUE
	PLACEBO	BOTULINUM TOXIN A	
Principal therapeutic target†			
Base line	2.52	2.70	0.04
Week 6	-0.31 (-0.48 to -0.14)	-0.94 (-1.16 to -0.72)	<0.001
Week 12	-0.46 (-0.67 to -0.24)	-0.88 (-1.12 to -0.63)	0.02
Muscle tone‡			
Wrist flexor			
Base line	3.13	3.11	0.79
Week 6	-0.48 (-0.66 to -0.30)	-1.66 (-1.87 to -1.44)	<0.001
Week 12	-0.31 (-0.48 to -0.14)	-1.07 (-1.30 to -0.84)	<0.001
Finger flexor			
Base line	3.05	3.06	>0.99
Week 6	-0.32 (-0.50 to -0.14)	-1.34 (-1.60 to -1.07)	<0.001
Week 12	-0.12 (-0.32 to -0.08)	-0.78 (-1.05 to -0.51)	<0.001
Thumb flexor			
Base line	2.28	2.46	0.28
Week 6	-0.62 (-0.95 to -0.28)	-1.31 (-1.63 to -0.98)	0.09
Week 12	-0.31 (-0.62 to -0.01)	-0.92 (-1.27 to -0.56)	0.02
Physician's global assessment§			
Week 6	0.57 (0.35 to 0.78)	1.77 (1.55 to 1.99)	<0.001
Week 12	0.50 (0.29 to 0.72)	1.09 (0.80 to 1.38)	<0.001
Patient's or caregiver's global assessment§			
Week 6	0.63 (0.40 to 0.85)	1.60 (1.30 to 1.89)	<0.001
Week 12	0.48 (0.25 to 0.72)	1.05 (0.76 to 1.34)	0.002

*For the principal therapeutic target and the muscle-tone scores, the data shown are changes from the base-line scores. The data for the physician's and patient's or caregiver's global assessments are the changes from pretreatment status. CI denotes confidence interval.

†The principal therapeutic target was chosen by each subject and a study investigator, and the effect of treatment on this target was measured with the use of the Disability Assessment Scale. A score of 0 indicates no disability, 1 mild disability, 2 moderate disability, and 3 severe disability. Thirty-two percent of the subjects chose dressing, 30 percent chose limb position, 26 percent chose hygiene, and 12 percent chose pain as the principal therapeutic target.

‡Muscle tone was measured with the use of the Ashworth scale. A score of 0 denotes no increase in muscle tone, 1 a slight increase, 2 a more marked increase, 3 a considerable increase, and 4 rigid flexion.

§The physician's and patient's or caregiver's global assessments of the response to treatment were determined with the use of the Global Assessment Scale. A score of -4 denotes very marked worsening, -3 marked worsening, -2 moderate worsening, -1 mild worsening, 0 no change, +1 mild improvement, +2 moderate improvement, +3 marked improvement, and +4 very marked improvement.

jects who received placebo ($P < 0.001$ for all comparisons). The maximal difference between the two groups in the mean change from base line occurred at week 4 (wrist score, -1.78 in the botulinum-toxin group and -0.42 in the placebo group; finger score, -1.59 and -0.27). In addition, subjects treated with botulinum toxin A had significantly greater improvement in flexor tone in the thumb at weeks 1, 4, 8, and 12 ($P < 0.001$, $P < 0.001$, $P = 0.002$, and $P = 0.02$, respectively).

The scores for the physician's global assessment were significantly higher in the botulinum-toxin group than in the placebo group at all five follow-up visits ($P < 0.001$). The scores for the patient's or caregiver's global assessment were also significantly higher in the botulinum-toxin group (weeks 1, 4, and 6, $P < 0.001$; weeks 8 and 12, $P = 0.002$). The proportion of subjects with at least a one-point improvement in the score for the physician's global assessment ranged from 67 to 91 percent in the botulinum-toxin group, as compared with only 27 to 44 percent in the placebo group ($P < 0.001$ for each comparison). At week 6, 67 percent of the subjects who received botulinum toxin A had at least a two-point increase in the score for the physician's global assessment, as compared with 11 percent of the subjects who received placebo ($P < 0.001$). Similarly, a larger proportion of subjects in the botulinum-toxin group than in the placebo group had at least a one-point increase in the score for the patient's or caregiver's global assessment at all five visits (67 to 81 percent of subjects in the botulinum-toxin group and 29 to 48 percent of those in the placebo group, $P < 0.001$). At week 6, 53 percent of the subjects in the botulinum-toxin group had at least a two-point increase in the score for the patient's or caregiver's global assessment, as compared with 15 percent of the subjects in the placebo group ($P < 0.001$).

Principal Therapeutic Target

At six weeks, the score on the Disability Assessment Scale for the principal therapeutic target was correlated with the composite scores on the Ashworth Scale for muscle tone in the wrist and fingers ($r = 0.61$, $P < 0.001$), the score for the physician's global assessment ($r = -0.46$, $P < 0.001$), and the score for the patient's or caregiver's global assessment ($r = -0.51$, $P < 0.001$). In addition, the change in the score for the principal therapeutic target was associated with the change in the scores for the physician's and the patient's or caregiver's global assessments ($P < 0.001$ for both correlations at all post-treatment visits).

Safety

There were no significant differences between the study groups in the incidence of specific adverse events (Table 3). There were also no clinically significant

changes in biochemical or hematologic variables during the 12-week follow-up period.

Neutralizing Antibodies

None of the subjects had been treated with any form of botulinum toxin before enrollment in the study. Post-treatment serum samples sufficient for analysis were obtained from 93 subjects, only 1 of whom had a positive test for neutralizing antibodies. This subject, who was assigned to the botulinum-toxin group, had no change in muscle-tone or disability scores and no adverse events associated with treatment. Since the serum sample obtained at base line was insufficient for analysis, the antibody status of the subject before treatment was unknown.

DISCUSSION

This large, multicenter, controlled study showed that in subjects with focal spasticity of the wrist and fingers due to a stroke, a single set of injections of botulinum toxin A into the spastic muscles resulted in significantly greater improvement in functional disability than did placebo injections. Botulinum toxin A had positive effects on functional disability throughout the 12-week study. In addition, botulinum toxin A significantly reduced flexor muscle tone in the wrist, fingers, and thumb and improved the scores for both the physician's and the patient's or caregiver's global assessment.

Clinicians have emphasized the importance of identifying patient-specific treatment goals, as opposed to providing treatment aimed solely at reducing muscle tone.¹⁷⁻²¹ In 1974, Landau stressed that successful rehabilitation requires an evaluation "of those symptoms that are disabling and those that are not."²² Several previous studies have shown no significant effects of botulinum toxin A on functional disability or have

TABLE 3. ADVERSE EVENTS.

EVENT*	PLACEBO	BOTULINUM
	(N=62)	TOXIN A (N=64)
		no. of patients (%)
Pain	4 (6)	5 (8)
Arm pain	2 (3)	4 (6)
Headache	2 (3)	4 (6)
Dizziness	1 (2)	4 (6)
Muscular weakness	0	4 (6)
Incoordination	8 (13)	3 (5)
Infection	6 (10)	3 (5)
Ecchymosis	4 (6)	2 (3)
Hypoesthesia	4 (6)	2 (3)

*Events reported by at least four patients or their caregivers in either group are shown.

shown minor changes on only one of several measures of functioning.^{3,4,7,8} These results may have been due to samples that were small or heterogeneous or to the use of measures with inadequate sensitivity for assessing changes in functional disability. Several investigations have shown a discrepancy between patients' perception of improvement and scores on standardized disability measures.^{6,7,17} For instance, in a study of repeated injections of botulinum toxin A, disability scores were unchanged but the patients achieved their goals for self-care.⁶ Unlike previous studies, ours was designed to assess specific improvement in an area of functioning that subjects identified as most important to them. Our finding that treatment with botulinum toxin A resulted in significantly greater improvement in the selected area of functioning than did placebo suggests that analysis of areas of functioning that are important to patients, as represented on the Disability Assessment Scale, may reveal benefits associated with patients' satisfaction and overall subjective experience of improvement.^{4,6}

In both our study and a previous double-blind study that showed improvements in functioning with the use of botulinum toxin A for spasticity, the analysis included hygiene and dressing as key variables.⁹ Deficits in these areas may be particularly disabling and may be amenable to treatment with botulinum toxin A. However, almost one third of the subjects in our study selected limb position as the principal therapeutic target. Its measurement may represent an advantage of the Disability Assessment Scale over other functional scales.

In our study, clinically meaningful and statistically significant improvements in the tone of the wrist and finger flexors, as measured by the Ashworth Scale, and an overall response to treatment were observed 1 week after the injections had been administered, and these changes were sustained throughout the 12-week follow-up period. (A videotaped example of the effect of treatment with botulinum toxin A, in a patient who was not enrolled in our study, is available as Supplementary Appendix 1 with the full text of this article at <http://www.nejm.org>.) Furthermore, an open-label extension of the study, in which 111 of the 126 subjects (88 percent) volunteered to receive up to three additional treatments, showed that each subsequent set of injections had positive effects that lasted for at least 12 weeks and in many cases for 18 to 24 weeks.²³ A study of repeated injections of botulinum toxin A for the treatment of upper-extremity spasticity showed a response that lasted for two to three years.⁶

Injections of botulinum toxin A also appeared to be safe in our subjects. This finding is consistent with the localized effect of botulinum toxin A, which minimizes the risk of systemic adverse events. Neutralizing antibodies developed in only one subject in our study

who was treated with botulinum toxin A. This subject did not have an improvement or a worsening of muscle tone or spasticity-related disability and did not have any adverse events. It is uncertain whether the antibodies were present before the subject received botulinum toxin A.

Our findings suggest that botulinum toxin A may be useful in improving flexor tone, functional disability, and quality of life in patients with spasticity of the fingers and wrist after a stroke.

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Dr. Jenkins and Ms. Mai Do are former Allergan employees. Dr. Turkel and Mr. Lee are current Allergan employees, and they and Dr. Jenkins have received stock options. Drs. Brashear, Gordon, Elovic, Kassich, and Marciniak have received research grants from Allergan. Drs. Brashear, Gordon, and Elovic have received honorariums for speeches from Allergan.

APPENDIX

In addition to the authors, the following investigators participated in the Botox Post-Stroke Spasticity Study Group: P.D. Charles, Vanderbilt University, Nashville; J. Cooper, East Bay Neurology, Berkeley, Calif.; D. Good, Wake Forest University Baptist Medical Center, Winston-Salem, N.C.; G.D. Graham, Health South Rehabilitation, Albuquerque, N.M.; A. Kirsteins, Charlotte Institute of Rehabilitation, Charlotte, N.C.; S. Pierson, Health South Braintree Hospital, Braintree, Mass.; M. Reding, Burke Rehabilitation Hospital, White Plains, N.Y.; G. Sheean, Neuromuscular Program, University of California, San Diego; K. Silver, University of Maryland Medical Systems, Baltimore; J. Stenehjem, Saddleback Medical Research Services, La Mesa, Calif.; T. Subramanian, Emory Clinic/Department of Neurology, Atlanta; R. Trosch, Clinical Neuroscience Center, Southfield, Mich.; J. Wald, University of Michigan Medical Center, Ann Arbor; and R. Zafonte, Rehabilitation Institute of Michigan, Detroit.

REFERENCES

1. Kurtzke JE. The current neurologic burden of illness and injury in the United States. *Neurology* 1982;32:1207-14.
2. Mayer NH, Esquenazi A, Childers MK. Common patterns of clinical motor dysfunction. *Muscle Nerve Suppl* 1997;6:S21-S35.
3. Simpson DM, Alexander DN, O'Brien CF, et al. Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial. *Neurology* 1996;46:1306-10.
4. Sampaio C, Ferreira JJ, Pinto AA, Crespo M, Ferro JM, Castro-Caldas A. Botulinum toxin type A for the treatment of arm and hand spasticity in stroke patients. *Clin Rehabil* 1997;11:3-7.
5. Bakheit AMO. Management of muscle spasticity. *Crit Rev Phys Rehabil Med* 1996;8:235-52.
6. Lagalla G, Danni M, Reiter F, Ceravolo MG, Provinciali L. Post-stroke spasticity management with repeated botulinum toxin injections in the upper limb. *Am J Phys Med Rehabil* 2000;79:377-84.
7. Smith SJ, Ellis E, White S, Moore AP. A double-blind placebo-controlled study of botulinum toxin in upper limb spasticity after stroke or head injury. *Clin Rehabil* 2000;14:5-13.
8. Wissel J, Muller J, Dressnandt J, et al. Management of spasticity associated pain with botulinum toxin A. *J Pain Symptom Manage* 2000;20:44-9.
9. Bhakta BB, Cozens JA, Chamberlain MA, Bamford JM. Impact of botulinum toxin type A on disability and carer burden due to arm spasticity after stroke: a randomised double blind placebo controlled trial. *J Neurol Neurosurg Psychiatry* 2000;69:217-21. [Erratum, *J Neurol Neurosurg Psychiatry* 2001;70:821.]
10. Ashworth B. Preliminary trial of carisoprodol in multiple sclerosis. *Practitioner* 1964;192:540-2.
11. Brin MF. Dosing, administration, and a treatment algorithm for use of botulinum toxin A for adult-onset spasticity. *Muscle Nerve Suppl* 1997;6:S208-S220.
12. Childers MK, Brashear A, Jozefczyk PB, et al. A multicenter, double-blind, placebo-controlled dose response trial of botulinum toxin type A (Botox) in upper limb spasticity post-stroke. *Neurology* 1999;52:Suppl 2:A295. abstract.
13. Brashear A, Zafonte RD, Lee C, Kuhn ER, Turkel C. The inter-rater and intra-rater reliability of the Ashworth Scale and Disability Assessment

Scale in patients with upper-limb post-stroke spasticity. *Arch Phys Med Rehabil* (in press).

14. Albright AI, Barron WB, Fasick MP, Polinko P, Janosky J. Continuous intrathecal baclofen infusion for spasticity of cerebral origin. *JAMA* 1993;270:2475-7.
15. Naumann M, Yakovlev A, Durif F. A randomized, double-masked, crossover comparison of the efficacy and safety of botulinum toxin type A produced from the original bulk toxin source and current bulk toxin source for the treatment of cervical dystonia. *J Neurol* 2002;249:57-63.
16. Hatheway CL, Dang C. Immunogenicity of the neurotoxins of *Clostridium botulinum*. In: Jankovic J, Hallett M, eds. *Therapy with botulinum toxin*. New York: Marcel Dekker, 1994:93-107.
17. Richardson D, Sheean G, Werring D, et al. Evaluating the role of botulinum toxin in the management of focal hypertonia in adults. *J Neurol Neurosurg Psychiatry* 2000;69:499-506.
18. Young RR. Spasticity: a review. *Neurology* 1994;44:Suppl 9:S12-S20.
19. Bakheit AM, Thilmann AF, Ward AB, et al. A randomized, double-blind, placebo-controlled, dose-ranging study to compare the efficacy and safety of three doses of botulinum toxin type A (Dysport) with placebo in upper limb spasticity after stroke. *Stroke* 2000;31:2402-6.
20. Klaiman MD. Current trends in the management of spasticity. *Trauma* 1997;39:33-49.
21. Gormley ME Jr, O'Brien CF, Yablon SA. A clinical overview of treatment decisions in the management of spasticity. *Muscle Nerve Suppl* 1997;6:S14-S20.
22. Landau WM. Spasticity: the fable of a neurological demon and the emperor's new therapy. *Arch Neurol* 1974;31:217-9.
23. Gordon MF, Brashear A, Elovic E, et al. A multicenter, open-label study of the safety and efficacy of repeated botulinum toxin type A doses in poststroke, focal, upper limb spasticity. *Neurology* 2002;58:Suppl 3: A221. abstract.

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CORRECTION

Botulinum Toxin for Spasticity after Stroke

To the Editor: The design of the study by Brashear et al. of botulinum toxin for stroke (Aug. 8 issue)¹ fails to meet the claim of a “double-blind, placebo-controlled trial.” The investigators were open partners with the manufacturer in conducting a study in which the outcome measures were patients’ reports of qualitative improvement after a dramatic injection that produces weakness. Whether the injection is paralytic or placebo, patients are likely to be biased toward reports of better performance and physicians toward observations of decreased reaction to flexor-muscle stretch. Thus, the 27 percent response to placebo is no surprise. Observation of true muscle weakness by both patients and physicians after the injection of toxin must inevitably reinforce this subjective sense of improvement.

The study lacked an essential blind crossover component. If, for example, patients were videotaped in the process of dressing on several occasions after the injection of drug and after the injection of placebo, unprejudiced observers who did not know the patients could have served to validate the presence of a therapeutic effect. Reports of conventional clinical tests of agility and coordination might have provided information about the physiologic mechanisms behind subjective improvement. Other interventions, such as physical therapy, splinting, and medication, which may affect outcomes, were not mentioned.

This study does not justify extended injections for most patients with stroke. As Rowland observes in the accompanying Perspective,² treatment of spasticity is a popular and profitable practice. But no well-controlled outcome studies have yet shown that the suppression of reflexes by drugs (baclofen or tizanidine), surgery, or physical therapy “can significantly improve coordinated movement in hemiplegic limbs.”^{3,4,5,6}

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References

1. Brashear A, Gordon MF, Elovic E, et al. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *N Engl J Med* 2002;347:395-400.
2. Rowland LP. Stroke, spasticity, and botulinum toxin. *N Engl J Med* 2002;347:382-383.
3. Landau WM. Spasticity: the fable of a neurological demon and the emperor’s new therapy. *Arch Neurol* 1974;31:217-219.
4. Burke D. Spasticity as an adaptation to pyramidal tract injury. *Adv Neurol* 1988;47:401-423.
5. Landau WM. Tizanidine and spasticity. *Neurology* 1995;45:2295-2296.
6. Landau WM. Muscle tone: hypertonus, spasticity, rigidity. In: Adelman G, Smith BH, eds. *Encyclopedia of neuroscience*. 3rd ed. New York: Elsevier Science, 2001.

To the Editor: Patients with chronic hemiplegic effects of stroke and physicians may interpret the study of Brashear et al. as showing that functional disability decreased, so functional ability to use the hand must have increased. The authors use the term “disability” in a fashion that requires close reading. The clinical effectiveness of the intervention can be summed up as a means to loosen the wrist and finger flexors, so that the hand is easier to maintain open passively. The study was powered to detect a change of 0.5 point on the Ashworth Scale of tone — a moot change in terms of clinical effectiveness. The small absolute but statistically significant changes in scores on the Disability Assessment Scale are a subjective measure of a narrow band of disability: patients’ perceptions about odd arm postures, difficulty in cleaning a clenched hand, pain possibly related to stiffness, and dressing skills not necessarily requiring the use of the affected hand. The authors offer no information about sensorimotor impairment or functionality of the hand for grasping and reaching before and after treatment. Did the subjects use the affected hand in performing daily activities before or after receiving injections?

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To the Editor: Brashear et al. report that patients assigned to injections of botulinum toxin type A “had greater improvement in the principal target of treatment than did subjects who received placebo” but do not report the actual degree of benefit seen in each of the four measures of disability. Can they provide these data?

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The authors reply: In response to Dr. Landau’s comments regarding our study, consideration was given to the issue of blinding. The source of funding for the study and the relationships between the investigators and the sponsor were clearly defined in our article in a manner that is consistent with the policy of the *Journal*. We do not believe that the results were biased.

Landau and Dobkin suggest videotaping, tests of agility, or sensorimotor or functional testing before and after injection. No data on sensorimotor impairment or specific functionality of the hand before treatment were obtained in this study. Videotaping was not used because

it does not have the sensitivity to detect a change. Functional testing may not be appropriate, since negative symptoms of the upper motoneuron syndrome (e.g., weakness) prevent voluntary, goal-directed movement, irrespective of the presence or absence of spasticity.¹ The Disability Assessment Scale measures a range of variables and is an appropriate first step in understanding the effects of the toxin treatment.

Clinically meaningful end points were explored in the development of this assessment scale. Input from patients and physicians indicates that for many, a primary goal is to reduce muscle tone, not necessarily to improve the active function of the affected limb.

A difference between groups in the mean change on the Ashworth Scale of tone that is smaller than that which we observed with botulinum toxin A has been considered to demonstrate the effectiveness of oral antispasticity treatment.² With regard to concomitant medication and physical therapy, both treatment groups were asked to maintain the regimens they had been receiving before the study.

We reported the results of a single treatment with botulinum toxin A and mentioned the results of an open-label extension of the study. Readers should wait for those results to be published before concluding that our "study does not justify extended injections for most patients with stroke."

The data requested by Drs. Buitrago and Koolwijk are listed in Table 1. Pain was not a primary symptom for the majority of patients; thus, it would be inappropriate to draw population-based conclusions.

We also wish to make the following corrections. The primary end point of this study, according to the protocol, was the change in the tone of the wrist flexor muscle from base line to week 6. Assessment of functional disability was an additional prespecified end point; week 6 was considered the primary end point of interest. In addition, on page 397, the fifth line of the section on "Efficacy" should read "62 in the placebo group" rather than "64 in the placebo group."

Table 1. Mean Scores at Base Line and Mean Change at Week 6 for All Variables According to the Disability Assessment Scale.

Table 1. Mean Scores at Base Line and Mean Change at Week 6 for All Variables According to the Disability Assessment Scale.

Variable	Botulinum Toxin		P Value
	Type A (N=64)	Placebo (N=62)	
Hygiene			
Base-line score	1.89	1.69	0.33
Week 6 change	-0.72	-0.14	0.004
Dressing			
Base-line score	2.25	1.94	0.04
Week 6 change	-0.49	-0.15	0.03
Pain			
Base-line score	0.78	0.94	0.27
Week 6 change	-0.37	-0.25	0.72
Limb position			
Base-line score	2.03	1.92	0.73
Week 6 change	-0.62	-0.24	0.02

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References

1. Mayer NH, Esquenazi A, Childers MK. Common patterns of clinical motor dysfunction. In: Mayer NH, Simpson DM, eds. Spasticity: etiology, evaluation, management, and the role of botulinum toxin. New York: WE MOVE, 2002:16-26.
2. Wallace JD. Summary of combined clinical analysis of controlled clinical trials with tizanidine. *Neurology* 1994;44:Suppl 9:S60-S69.