therapy of skull base tumors. Int J Radiat Oncology Biol Phys 1997;38:231–239.

5. Vigliani MC, Sichez N, Poisson M, et al. A prospective study of cognitive functions following conventional radiotherapy for supratentorial gliomas in young adults: 4-year results. Int J Radiat Oncol Biol Phys 1996;35:527–533.

6. Armstrong C, Ruffer J, Corn B, et al. Biphasic patterns of memory deficits following moderate-dose partial-brain irradiation: neuropsychologic outcome and proposed mechanisms. J Clin Oncol 1995;13:2263–2271.

7. Gregor A, Cull A, Traynor E, et al. Neuropsychometric evaluation of long-term survivors of adult brain tumors: relationship with tumour and treatment parameters. Radiother Oncol 1996;41:55–59.

8. Taphoorn MJB, Schiphorst AK, Snoek FJ, et al. Cognitive functions and quality of life in patients with low-grade gliomas: the impact of radiotherapy. Ann Neurol 1994;36:48–54.

9. Kleinberg L, Wallner K, Malkin MG. Good performance status of long-term disease-free survivors of intracranial gliomas. Int J Radiat Oncol Biol Phys 1993;26:129–33.

10. Imperato JP, Paleologos NA, Vick NA. Effects of treatment on long-term survivors with malignant astrocytomas. Ann Neurol 1990;28:818–822.

11. Vigliani MC, Duyckaerts C, Hauw JJ, et al. Dementia following treatment of brain tumors with radiotherapy administered alone or in combination with nitrosourea-based chemotherapy: a clinical and pathological study. J Neurooncol 1999;41:137–149.

12. DeAngelis LM, Delattre JY, Posner JB. Radiation-induced dementia in patients cured of brain metastases. Neurology 1989;39:789–796.

13. Wechsler D. Manual for the Wechsler Adult Intelligence Scale. New York: The Psychological Corporation, 1955.

14. Vilkki J. Perseveration in memory for figures after frontal lobe lesion. Neuropsychologia 1989;27:1101–1104.

15. Benton AL. The Revised Visual Retention Test: clinical and experimental applications. New York, NY: The Psychological Corporation, 1963.

16. Broderick JP, Brott TG, Duldner JE, et al. Volume of intracerebral hemorrhage: A powerful and easy-to-use predictor of 30-day mortality. Stroke 1993;24:987–993.

Botulinum toxin A and chronic low back pain

A randomized, double-blind study

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Article abstract—*Objectives:* To investigate the efficacy of botulinum toxin A in chronic low back pain and associated disabilities. *Methods:* Thirty-one consecutive patients with chronic low back pain who met the inclusion criteria were studied: 15 received 200 units of botulinum toxin type A, 40 units/site at five lumbar paravertebral levels on the side of maximum discomfort, and 16 received normal saline. Each patient's baseline level of pain and degree of disability was documented using the visual analogue scale (VAS) and the Oswestry Low Back Pain Questionnaire (OLBPQ). The authors reevaluated the patients at 3 and 8 weeks (visual analogue scale) and at 8 weeks (OLBPQ). *Results:* At 3 weeks, 11 of 15 patients who received botulinum toxin (73.3%) had >50% pain relief vs four of 16 (25%) in the saline group ($p = 0.012$). At 8 weeks, nine of 15 (60%) in the botulinum toxin group and two of 16 (12.5%) in the saline group had relief ($p = 0.009$). Repeat OLBPQ at 8 weeks showed improvement in 10 of 15 (66.7%) in the botulinum toxin group vs three of 16 (18.8%) in the saline group ($p = 0.011$). No patient experienced side effects. *Conclusion:* Paravertebral administration of botulinum toxin A in patients with chronic low back pain relieved pain and improved function at 3 and 8 weeks after treatment.

Nearly 90% of adults experience back pain at some point in their lives.[1] In the military, 20% of medical discharges are related to back symptoms. Approximately 70% to 90% of cases of acute low back pain resolve with nonspecific treatment within 5 weeks.[2] Chronic low back pain currently costs the American economy an estimated 50 billion dollars per year.[3] At present, effective pharmacologic therapy of chronic mechanical low back pain is limited to nonsteroidal anti-inflammatory agents, antispasmodic and antidepressive drugs, muscle relaxants, and opioids.[4]

Intramuscular injection of botulinum toxin A (Botox, Allergan, Inc., Irvine, CA) has been shown to be safe and relieves pain associated with several movement disorders,[5-7] chronic myofacial[8,9] and cervical pain syndromes.[10-12] We investigated the efficacy of

paravertebral injection of Botox (Allergan, Inc.) in patients with chronic low back pain.

Methods and design. The sample size determination proposed in the original protocol was based on a previous study of the effect of a fitness program on chronic low back pain.[13] Controlling the probability of type I error at $\alpha = 0.05$, a sample of 22 subjects in each group provided 80% power to detect a 50% improvement (ie, a 10-point difference using the criteria proposed by Frost et al.[13]) in Oswestry Low Back Pain Questionnaire (OLBPQ) scores between groups. We stopped our study after enrolling 31 patients because the author (L.F.) who was the source of patient referral moved from the area. The blind was broken only after final decision was made to stop the trial, not based on the results of partial analysis of the data.

The study comprised 15 men and 16 women. All signed an informed consent before participation. The selection criteria consisted of 1) low back (between L-1 and S-1) pain, 2) pain duration of 6 months or longer, and 3) pain laterality (either unilateral or if bilateral, showing a left or right predominance). Exclusion criteria included low back pain of less than 6 months duration, age under 18 years, presence of a systemic inflammatory disorder, acute pathology on MRI, known allergy or sensitivity to Botox (Allergan, Inc.), current or planned pregnancy, disorders of neuromuscular transmission, and anesthetic or corticosteroid injections to the lumbosacral spine within 12 weeks of enrollment. Patients involved in litigation, seeking significant disability for low back pain, or with evident secondary gain were also excluded from the study. All exclusions were performed before trial entry. The patients were on a variety of analgesic and antispasmodic medications, including baclofen, nonsteroidal anti-inflammatory drugs, antidepressants, and muscle relaxants. They were advised to continue their medications and not to change the dose during the study.

A physiatrist (L.F.) referred most of the patients for this study and performed the clinical rating. He documented the physical findings, screened the patients for exclusion criteria, and described the location and the side predominance of pain, presence or absence of increased paravertebral muscle tone, back tenderness, and focal trigger points (when present). Patients completed an intake questionnaire depicting background information including age, gender, mechanism of injury (if known), prior treatments, compensation issues, and general medical and psychological history.

A majority of the patients disclosed no clear causative or precipitating factor. Six had a history of disc disease and three had had discectomy 5 to 18 years prior to this study. Four patients had a history of remote low back trauma. MRI revealed chronic changes related to previous surgery in three and disclosed evidence of degenerative spine disease in four older patients. In no patient did MRI show acute pathology.

The pain was described as "severe ache," "like a bad toothache," "deep discomfort," or "jabbing." Seven patients had unilateral back pain. Others had bilateral pain but the pain was noticeably more severe on one side.

A nurse clinician not familiar with the patients randomly assigned them to Botox (Allergan, Inc.) and placebo groups by drawing a card from a deck of shuffled cards

Registered Eligible Patients (n=31)

Not Randomized (n=0)
Randomized (n=31)

Received botulinum toxin A (n=15)   Received placebo (n=16)

Follow up (n=14)   Follow up (n=14)
Three weeks, Two months   Three weeks, Two months

Withdrawn (n=1)   Withdrawn (n=2)
Lost to follow up   Lost to follow up

Completed trial (n=14)   Completed trial (n=14)

Figure. Flow diagram shows number of patients who enrolled in the trial, the number in each group, duration of follow-up, and the number that completed the study.

that included equal number of Botox (Allergan, Inc.) and saline cards. The allocation was concealed by calling a central trial office that kept the allocation data in sequential numbered and sealed folders. The physician who examined and rated the patients, other physicians involved in the study, and the patients were blinded to the content of injected solution. The nurse clinician who prepared the solution was the sole person who knew the content of the syringe and kept a concealed record.

The rater used a visual analogue scale (VAS)[13] to measure the level of each patient's pain and the OLBPQ to assess the degree of physical impairment and disability. The VAS consisted of a 10-cm horizontal line with two points labeled "no low back pain" and "worst low back pain." Subjects were requested to mark the line at a point corresponding to the level of pain they generally experienced. The distance in centimeters (1 to 10) from the low end of the VAS to the subject's mark was used as numeric index of severity of pain and pain change.

The OLBPQ is a questionnaire that requests information about functional ability regarding tasks of daily living. It consists of 10 different subsets: pain, personal care (dressing, washing, etc), lifting, walking, sitting, standing, sleeping, sex, social life, and traveling. Each subset is graded from 0 to 5, 0 being normal and 5 being most affected. The VAS and OLBPQ have been found to be valid, internally consistent, and reliable measures of pain and disability in patients with low back pain.[14,15]

Botulinum toxin A (Allergan, Inc.) was prepared by reconstituting freeze-dried toxin with preservative-free 0.9% saline to 100 units/mL concentration. The material was drawn into a 1 mL-tuberculin syringe and injected through a 27-gauge needle. Injections (Botox or saline) were given at five lumbar (L-1 to L-5) or, if pain involved the upper sacral region, lumbosacral (L-2 to S-1) sites; each site received 40 units. All patients were injected only once unilaterally on the side of pain or pain predominance.

The reconstituted Botox (Allergan, Inc.) solution is colorless and cannot be distinguished from saline. Like saline, it causes no pain when administered intramuscularly.

The physician-rater recorded the results of VAS at baseline (before treatment) and at 3 and 8 weeks after treatment. The OLBPQ was filled out at baseline and reevaluated once after 8 weeks. Patients were asked to report side effects anytime, specifically at 3 and 8 weeks.

Table *Demographic data of 31 randomized patients*

Patients	Saline	Botulinum toxin A
Sample size, n	16	15
M/F	8/8	7/8
Mean age (range), y	47.0 (20–73)	46.4 (21–65)
Mean (range) duration of pain, y	5.7 (0.5–20)	8.1 (1–30)
Patients with tender points, n	12 (between L-1 and S-1)	11 (between L-2 and S-1)
Patients with trigger points, n	1	2
Patients with spasms, n	2 (1 during injection)	2 (2 during injection)
Patients who had surgery (L-5–S-1 disc), n	2 (1 had surgery)	4 (2 had surgery*)
Patients with neurologic deficits, n†	2	3

* Both demonstrated significant pain relief after administration of Botox.

† Unilateral or bilateral absent ankle jerks, or L-5 or S-1 segmental sensory deficits.

All primary outcome variables were specified before unblinding and data analysis.

Data analysis. For VAS, the clinical response was considered significant when the difference (improvement) between pre- and post-treatment scores was at least 50%. For OLBPQ, we defined a significant functional improvement as at least a two-grade improvement over the baseline (pretreatment) value in one or more functional subset (in addition to the pain subset). The primary analysis of the data was an intention-to-treat analysis comparing patient groups according to random assignment. The primary variables were pain and functional units measured by VAS and OLBPQ. Significant response to pain and improvement of functionality was compared between groups using the Fisher's exact test (two-tailed). The p values and CI were calculated. To allow for comparison of three outcomes, a Bonferroni-adjusted p value of less than 0.0167 (0.05/3) was considered significant.

Results. Twenty-eight of 31 patients completed the study, as shown in the figure. The study group had a mean age of 46 years (range, 20 to 73) and a mean pain duration of 6 years (range, 6 months to 30 years).

The intensity of pretreatment pain measured by VAS varied from 6 to 10 (mean, 7.5) in the Botox group and 5 to 10 (mean, 7) in the saline group. The pretreatment OLBPQ showed functional impairments in one to seven subsets (in addition to the pain subset) with no significant difference between two groups (Botox or saline). For analysis of the data, we considered the three patients who did not report for follow-up as nonresponders. At 3 weeks, 13 of 15 patients (86%) in the Botox group and five of 16 patients (31%) in the saline group reported some degree of pain relief. The degree of relief exceeded 50% (VAS score) in 11 of 15 patients (73.3%) in the Botox group compared with four of 16 (25%) in the saline group ($p = 0.012$). The differ-

ence between these groups was 48% (95% CI, 11.7% to 80.1%). At 8 weeks, nine of 15 patients (60%) in the Botox group and two of 16 (12.5%) in the saline group reported pain relief exceeding 50% ($p = 0.009$), a difference of 47.5% (95% CI, 10.5% to 79.1%). For the OLBPQ, 10 of 15 patients (66.7%) in the Botox group and three of 14 (18.8%) in the saline group demonstrated improvement at 8 weeks ($p = 0.011$). The difference between groups was 47.9% (95% CI, 10.9% to 79.6%).

No patient had worsening of pain or function after Botox administration. Two patients reported worsening of pain after saline administration. Injections were well tolerated by all patients and none had side effects. Six of 10 responders in the Botox group who could be reevaluated at 6 months reported cessation of the analgesic effect after 3 and 4 months. The table shows the sample size, sex, age, pain duration, neurologic findings, and previous surgery in the two groups.

Discussion. Increased paraspinal muscle activity has been implicated as a factor in low back pain.[16] Pain may arise within the ischemic overactive muscle itself due to the build-up of metabolic waste products or from structures around the muscle (such as joints and tendons) stressed by persistent muscle tension. Electromyographic studies often demonstrate increased electrical activity of the paraspinal muscles during activity in patients with low back pain compared with subjects without pain.[16-19] The mechanical stretch of paraspinal muscles in patients with low back pain often provokes localized back pain.[20] The possibility that overactive paraspinal muscles may contribute to low back pain provides a rationale for treatment strategies aimed at reducing paraspinal muscular tone, such as biofeedback and muscle relaxing drugs. Although data supporting the effectiveness of biofeedback in low back pain are limited, muscle relaxants including benzodiazepines[21] and cyclobenzaprine[22] have been shown to provide a measure of relief.

In our patients, significant reduction of low back pain following Botox (Allergan, Inc.) treatment might have resulted from one or more of the following:

1. Significant reduction of muscle spasms;[6,7] four of our patients had severe paravertebral muscle spasms.

2. Reduction of intrafusal muscle spindle discharges,[23] which convey non-nociceptive sensations to the spinal cord. It is believed that in chronic pain conditions, persistence of pain partly results from sensitization of "wide dynamic range neurons" in the cord that then may perceive the non-nociceptive input as nociceptive.[24]

3. Impairment of sympathetic transmission.[25] Some studies have indicated that activity in axons located in the lumbar sympathetic chain contributes to the activation of the spinal pathways and to low back pain.[26]

4. Reduction of the inhibitory effect of Renshaw cells on the Ia inhibitory interneurons, as shown in animals.[27]

5. Indirect effects on spinal cord neurons. In one study, autoradiography showed presence of radiola-

beled botulinum toxin in the ipsilateral ventral roots and ipsilateral hemicord of the cat, 48 hours after injection of ^{125}I-labelled Botox (Allergan, Inc.) in one gastrocnemius muscle.[28] These indirect effects on spinal cord neurons may also be at work in humans after paravertebral treatment.

6. An analgesic effect of Botox metabolites.[29]

In a recent editorial review, Hallet[30] emphasized this as an important mechanism for the action of Botox in clinical disorders (including pain).

Possible impairment of ambulation (due to weakness of back muscles) after paravertebral injection concerned some investigators. The dose administered in this study caused no such effect and in fact some patients showed improved ambulation due to decreased pain. Comella et al.[31] also did not report any impaired ambulation in five patients with extensor truncal dystonia who were treated paravertebrally with doses comparable to that of our study (150 to 300 units/session). In a patient with stiff-person syndrome, repeated paravertebral muscle injections of Botox (Allergan, Inc.) in doses double that used here also caused no ill effects.[32]

To our knowledge, this is the first double-blind study to show the efficacy of Botox for treatment of low back pain. However, this conclusion should be considered cautiously, due to the small number of the patients studied. Further investigations are needed to determine if these findings can be reproduced in a larger number of patients or if this positive effect continues with repeated injections, as is the case for dystonias and spasticity.

References

1. Wipf JE, Deyo RA. Low back pain. Med Clin North Am 1995; 79:231–246.
2. Frymoyer JW. Predicting disability from low back pain. Clin Orthop Rel Res 1992;279:101–109.
3. Nachemson A. Newest knowledge of low back pain. Clin Orthop Rel Res 1992;279:8–20.
4. Bigos S, Bowyer O, Braen G. Acute low back problems in adults. Clinical Practice Guideline No. 14, AHCPR Publication No. 95-0642 ed. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services, 1994:160.
5. Greene P, Kang U, Fahn S, et al. Double blind, placebo controlled trial of botulinum toxin injection for the treatment of spasmodic torticollis. Neurology 1990;40:1213–1218.
6. Karp BI, Cole RA, Cohen LG, et al. Long-term botulinum toxin treatment of focal hand dystonia. Neurology 1994;44:70–76.
7. Grazko MA, Polo KB, Jabbari B. Botulinum toxin A for spasticity, muscle spasms, and rigidity. Neurology 1995;45:712–717.
8. Cheshire WP, Abashian SW, Mann JD. Botulinum toxin in the treatment of myofascial pain syndrome. Pain 1994;59:65–69.
9. Cavanaugh JM, Weinstein JN. Low back pain: epidemiology, anatomy and physiology. In: Wall PD, Melzack R, eds. Textbook of pain. 3rd ed. Edinburgh: Churchill Livingstone, 1994: 441–455.
10. Wheeler A, Goelkusian PA, Gretz SS. Randomized, double-blind, prospective pilot study of botulinum toxin injection for refractory unilateral, cervicothoracic, paraspinal, myofacial pain syndrome. Spine 1998;23:1662–1667.
11. Freund BJ, Schwartz M. Treatment of whiplash associated neck pain with Botox: report of 8 cases. J Rheumatol 1999;26: 756–8.
12. Dutton JJ. Botulinum toxin in treatment of craniocervical muscle spasms short and long term, local and systemic effects. Surv Ophthalmol 1996;41:51–65.
13. Frost H, Klaber Moffett JA, Moser JS, et al. Randomised controlled trial for evaluation of fitness programme for patients with chronic low back pain. BMJ 1995;310:151–154.
14. Price DD, Bush FM, Long S, et al. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. Pain 1994;56:217–226.
15. Fairbanks JCT, Couper J, Davies JB, et al. The Oswestry Low Back Pain Disability Questionnaire. Physiotherapy 1980;66: 271–273.
16. Nouwen A, Bush C. The relationship between paraspinal EMG and chronic low back pain. Pain 1984;20:109–123.
17. DeVries HA. EMG fatigue curves in postural muscles. A possible etiology for idiopathic low back pain. Am J Phys Med 1968;47:175–181.
18. Ravitz E, Moore ME, Glaros A. Paralumbar muscle activity in chronic low back pain. Arch Phys Med Rehabil 1981;62:172–176.
19. Sherman RA. Relationships between strength of low back muscle contraction and reported intensity of chronic low back pain. Am J Phys Med 1985;64:190–200.
20. Kuslich SD, Ulstrom CL, Michael CJ. The tissue origin of low back pain and sciatica: a report of pain response to tissue stimulation during operations on the lumbar spine using local anesthesia. Orthop Clin North Am 1991;22:181–187.
21. Horgorani K. Diazepam in backache: a double blind controlled trial. Ann Phys Med 1965;8:303–306.
22. Borenstein DG, Lacks S, Wiesel SW. Cyclobenzaprine and naproxen versus naproxen alone in the treatment of acute low back pain and muscle spasm. Clin Ther 1990;12:125–131.
23. Fillipi GM, Errico P, Santarelli R, et al. Botulinum A toxin effects on rat jaw muscle spindles. Acta Otolarynol 1993;113: 400–404.
24. Roberts WJ. A hypothesis on the physiological basis for causalgia and related pains. Pain 1986;24:297–311.
25. Rand MJ, Whaler BC. Impairment of sympathetic transmission by botulinum toxin. Nature 1965;206:588–591.
26. Gillette RG, Kramis RC, Roberts WJ. Sympathetic activation of cat spinal neurons responsive to noxious stimulation of deep tissues in the low back. Pain 1994;31:42.
27. Hagenah R, Benecke R, Wiegand H. Effects of type A botulinum toxin on the cholinergic transmission at spinal Renshaw cells and on the inhibitory action at Ia inhibitory interneurons. Naunyn Schmiedebergs Arch Pharmacol 1997;299:267–72.
28. Wiegand H, Erdmann G, Welhoner HH. 125I-labelled botulinum A neurotoxin: pharmacokinetics in cats after intramuscular injection. Naunyn Schmiedebergs Arch Pharmacol 1976; 292:161–165.
29. Guyer B. Mechanism of botulinum toxin in the relief of chronic pain. Curr Rev Pain 1999;3:427–431
30. Hallett M. How does botulinum toxin work. Ann Neurol 2000; 48:7–8.
31. Comella CL, Shannon K, Jaglin J. Extensor truncal dystonia. Successful treatment with botulinum toxin injections. Mov Disord 1998;13:552–555.
32. Davis D, Jabbari B. Significant improvement of stiff-person syndrome after paraspinal injection of botulinum toxin A. Mov Disord 1993;8:371–373.