

BRIEF RESEARCH REPORT

Treatment of Refractory, Chronic Low Back Pain with Botulinum Neurotoxin A: An Open-Label, Pilot Study

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ABSTRACT

Objective. To study the short- and long-term effects of botulinum neurotoxin A (BoNT-A, Botox[®], Allergan Inc.) on refractory chronic low back pain.

Design. The effect of botulinum neurotoxin A on chronic low back pain was prospectively studied in 75 patients with repeated treatments over a period of 14 months. Pain intensity (visual analog scale [VAS]), pain frequency (pain days), and perceived functional status (Oswestry scale) were assessed at baseline, 3 weeks, and at 2, 4, 6, 8, 10, 12, and 14 months. BoNT-A was injected into para-spinal muscles at 4–5 levels (between L1 and S1) unilaterally or bilaterally. The dose per site varied from 40 to 50 units. The total dose per session ranged from 200 to 500 units. Reinjections were performed at 4 months only when pain returned.

Results. At 3 weeks, 40 patients (53%) and at 2 months, 39 patients (52%) reported significant pain relief. The change in VAS, Oswestry score, and pain days was significant compared with baseline at 2 months after each injection period ($P < 0.005$) and remained so over subsequent treatments. Among initial responders, 91% continued responsiveness over the length of the study. Three patients (4%), after the first treatment, had a mild flulike reaction that lasted 2–5 days.

Conclusion. Botulinum neurotoxin A may be beneficial in patients with chronic low back pain. A favorable initial response predicts subsequent responsiveness. The treatment is well tolerated, and side effects are mild and transient.

Key Words. Low Back Pain; Botulinum Neurotoxin A; Botox; Root Pain

Introduction

Low back pain (LBP), a major health problem, accounts for 40% of all work-related compensation costs [1] and renders an annual burden (direct and indirect) of \$100 billion to the US economy [2]. Approximately 10% of all episodes of acute LBP develop into chronic one [3].

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Recently, a short-term, randomized, double-blind, placebo-controlled study in patients with chronic LBP has reported significant pain relief after injection of botulinum neurotoxin A into para-spinal muscles [4]. Short-term retrospective studies also suggested benefit from this form of treatment in chronic LBP [5,6].

In this communication, we report the results of a 14-month, open-label, prospective study evaluating the short- and long-term effects of para-spinal muscle injections of botulinum neurotoxin A (Botox[®] or BoNT-A, Allergan Inc., Irvine, CA) in patients with refractory, chronic LBP. The pur-

pose of this study was to address the following questions: 1) Can BoNT-A help patients with refractory LBP? 2) Does an initial favorable response to this agent predict a favorable long-term response? 3) Is repeated para-spinal administration of botulinum neurotoxin A safe?

Materials and Methods

Seventy-five patients were enrolled in this prospective open-label protocol. Patients were from a military hospital; active-duty soldiers, retired officers, and their spouses. They met the following inclusion criteria: 1) with LBP of at least 6-month duration; 2) aged 18 years or older; and 3) failure of standard medical or surgical treatment. Criteria for exclusion were: 1) abnormal lumbo-sacral magnetic resonance imaging (MRI) requiring urgent surgical or medical attention; 2) current or planned pregnancy; 3) disorders of neuromuscular transmission; 4) known allergy or sensitivity to BoNT-A; and 5) ongoing litigation. Patients with prior surgery were allowed in the study. Patients continued with their analgesic medication(s) during the study, but were instructed not to change the dose and avoid using new analgesics. They also continued with their physical therapy regimen as prescribed by routine clinical practice. Women of child-bearing age were screened for pregnancy with a urine pregnancy test. Informed consent was obtained on each patient and the study approved by the institutional review board.

During the first visit, patients were evaluated for enrollment by a nurse assigned to the study using the aforementioned inclusion/exclusion criteria. Those who met the criteria were seen by a neurologist who took history, performed physical examination, and documented the level of pain and perceived functional status by using three validated scales: visual analog scale (VAS—average and maximum), Oswestry low back pain questionnaire (OLBPQ), and pain impact questionnaire (PIQ). The patients then received their first treat-

ment in the same session. Follow-up visits were at 3 weeks and at 2, 4, 6, 8, 10, 12, and 14 months. VAS, OLBPQ, and PIQ values were documented in each subsequent visit (Table 1). VAS and OLBPQ were the primary outcome measures in this study. A secondary outcome measure was the number of pain days in PIQ. An initial response at 2 months was defined as significant when there was: a fall of 50% or more in the individual VAS maximum score, OLBPQ: demonstrated two or more level improvements in at least one functional subset (sitting, standing, sleeping, etc.) of the test in addition to the pain subset. The test has 10 subsets each graded into six levels (0 = no limitation, 5 = maximum limitation) and PIQ: >30% decrease in the number of pain days.

An individual VAS maximum was the maximum VAS score during 28 days preceding evaluation, while an individual VAS average was the mean of daily VAS scores for that individual over the preceding 28 days. The pain days score (a part of PIQ) was the number of pain days during the preceding 28 days, and the individual Oswestry score was the total score (maximum 50) for that individual during the day of evaluation.

Group differences (responder vs. baseline) were assessed by the Student's *t*-test. Here the mean values of all individual scores for that group of responders (at a given point of time—bimonthly intervals) were compared with that of the individual scores in the baseline group. For VAS average, this would be the mean of all individual means for that group.

Responders would be retreated with the same effective dose at 4-month intervals if the pain returned. Those who had no significant pain (supported by rating scales) after first 4 months would be evaluated for retreatment at 2-month intervals.

Botulinum neurotoxin A was prepared by combining vacuum-dried toxin with preservative-free 0.9% saline to a concentration of 100 units/mL. Injections were made through a 1-cc tuberculin syringe with 1.5-in, 27-gauge needle, unilaterally

Table 1 Timing of neur-exam, pain ratings, and Botex treatment

	Baseline	2 Months	4 Months	6 Months	8 Months	10 Months	12 Months	14 Months
Examination	X	X	X	x	X	X	X	X
VAS	X	X	X	x	X	X	X	X
OLBPQ	X	X	X	x	X	X	X	X
PIQ	X	X	X	x	X	X	X	X
Botox injection	X		X		X		X	

For most patients, Botox treatment was repeated at 4, 8, and 12 months. OLBPQ = Oswestry low back pain questionnaire; PIQ = pain impact questionnaire; VAS = visual analog scale.

or bilaterally, based on the predominant pattern of pain distribution. The first site of injection was selected to be at the vertebral level of most intense pain (defined by the patient and physician using deep finger pressure). Subsequent injection sites extended to at least one (and often two) level above and below the pain location. Thus, most patients were injected at five sites into para-spinal muscles between L1 and S1 vertebral levels. The rationale for this methodology was to cover as much as possible the length of para-spinal muscles, as superficial recti muscles are long and extend over several vertebral levels. When the area of pain extended laterally, one additional injection (same dose) was administered at the same level to a more lateral aspect of the paravertebral muscles. Injections were performed without electromyographic guidance. The dose per injection site was 50 units (40 units for very thin patients). The total dose per session ranged from 200 to 500 units, depending on presence of unilateral or bilateral pain. Patients were instructed to report side effects at any time during the study. Statistical significance and relevant *P* values were calculated by comparison with baseline scores in the three rating scales using the Student's *t*-test on spss software, version 12.0 (SPSS Inc., Chicago, IL).

Results

Seventy-five adults, 56 men, with a mean age of 46.1 years at the time of entry (range 21–79), were enrolled in the study. The pain duration varied from 7 months to 50 years (9.1 years). Sixty-five patients had bilateral pain (88%), 20 had root pain, and 22 had focal neurological deficits (mostly minor sensory). Fourteen patients had previous surgery, 15 had previous epidural injections, and 36 were on opioid medications. Thirty patients demonstrated muscle tenderness in deep finger pressure focally over the para-spinal region, with five expressing referred pain conforming to the definition of trigger points. Six patients had distinct muscle spasms. Lumbar MRI was abnormal in 71 of 75 patients (95%), with common abnormalities being single- or multi-level lumbar or lumbosacral chronic disc protrusions, canal narrowing and stenosis, degenerative changes, or a combination of these structural changes.

Short-Term Treatment Results

At 3 weeks, 40 (53%) and at 2 months, 39 (52%) of 75 patients demonstrated a significant response

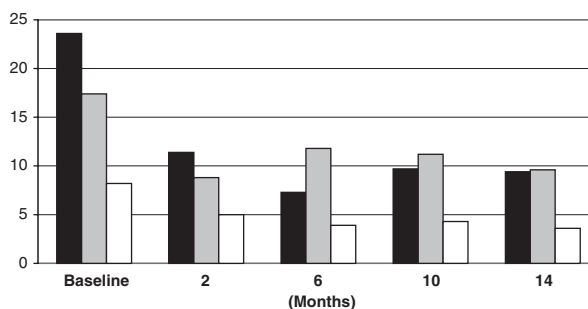


Figure 1 Mean pain days (PIQ)—dark, OLBPQ—gray and VAS—white, values before treatment and at 2 months after each treatment (injections are given at baseline and for most patients at 4, 8, and 12 months). Pain days and VAS maximum are assessed over preceding 28 days—VAS range: 0–100 mm, and the graph bar here is presented in centimeter, OLBPQ score range: 0–50. *P* values compare to baseline for all three measures (<0.005). OLBPQ = Oswestry low back pain questionnaire; PIQ = pain impact questionnaire; VAS = visual analog scale.

to BoNT-A treatment. At 2 months, mean group values for VAS average, VAS maximum, OLBPQ score, and pain days (in PIQ) 5.5, 8.4, 17.2, and 23.4 fell to 3.6, 5, 12.5, and 11.1, respectively ($P < 0.005$ for all values) (Figure 1). Responders reported the onset of therapeutic response within 24–96 h. Improvement of LBP was associated with improvement or cessation of local tenderness at the region of maximum pain. Four of six patients with distinct muscle spasms responded to treatment favorably. Nine of 20 patients with radicular pain (45%) also reported a significant improvement of the root pain. The pain totally stopped in six patients and was reduced to less than 20% of its intensity in three patients. In those patients whose root pain stopped after treatment, provoking maneuvers in physical examination could no longer elicit root pain. Comparing responders with nonresponders, there was no statistically significant difference between the two groups with respect to age, gender, pain intensity, pain duration, pain laterality, history of surgery, presence of radicular pain, focal muscle tenderness, neurological deficits, use of opioids, or the type of MRI abnormality.

Long-Term Treatment Results

Of 39 initial responders (at 2 months), 32 completed the trial. Seven patients (17%) were lost in follow-up. Two patients became nonresponders, one after the second and another after the third treatment. The two converters did not differ from

the rest of initial responders in regard to any of the factors depicted in Table 1. In one of these two subjects, the frontalis muscle test did not support antibody formation.

In responders, all scores remain improved over the period of follow-up and after each treatment. Figure 1 shows mean VAS, OLBPQ scores, and pain days (PIQ) for each group at baseline and at 2, 6, 10, and 14 months (2 months after each treatment for most patients).

Eleven of 30 responders (36%) who finished the 14-month follow-up reported that first favorable response lasted beyond 4 months. In six patients the response lasted 6 months, in four patients 8 months, and one patient did not feel the need for reinjection over the length of the study.

Three patients (4%) reported side effects. These were mild, flulike reactions with a duration of 3–5 days. They required no specific treatment. Two of the three who were responders had this reaction only after the first treatment.

Discussion

Botulinum neurotoxin A is a potent inhibitor of acetylcholine release as well as a number of other neurotransmitters and neuropeptides. In humans, the analgesic effect of BoNT-A was first demonstrated after observing significant pain relief in cervical dystonia (torticollis) [7,8]. Although the antispasticity and antidystonic effects of Botox are often attributed to blockade of acetylcholine release from pres-synaptic vesicles, recent animal studies suggest other analgesic mechanisms for this neurotoxin: anti-inflammatory effects and glutamate neurotransmitter inhibition [9], reduction of central sensitization by diminishing sensory input to spinal cord neurons [10], attenuation of sympathetic and parasympathetic output [11,12], prevention of substance P release [13], and possibly a direct effect upon spinal cord neurons [14]. Many of these factors are thought to play a role in the pathophysiology of chronic LBP [15–17].

A limitation of our study is the heterogeneity of the diagnosis and the involved mechanisms. In a heterogeneous group, the pain can be caused by a variety of factors. A common cause is myofascial pain syndrome (MFPS), which often responds to botulinum neurotoxin A treatment [18]. MFPS is characterized by presence of trigger points, taut muscle bands, and muscle spasms [19]. Although a few of our patients probably had MFPS, we do not believe that our cohort's favorite response was

predominantly related to it as majority of the responders did not have trigger points or muscle spasms.

The study presented here can be construed as an extension of our previous, double-blind, placebo-controlled report suggesting efficacy of botulinum neurotoxin A in chronic LBP [4]. In that study, at 2 months, 60% of the patients who received BoNT-A demonstrated significant pain relief compared with only 12.5% in the saline group ($P < 0.05$). Although our current open-label study can not prove efficacy, continued responsiveness of majority of initial responders (91%) suggests that the drug has a beneficial effect. The treatment also proved safe with minor and transient side effects over the follow-up period of 14 months.

There were other observations of practical importance and interest in this study:

1. Over one third (36%) of initial responders did not need a second treatment before 6 months, a finding of fiscal importance in view of the high cost of botulinum neurotoxin A therapy. Prolonged responses are increasingly recognized in other applications of BoNT-A therapy. Different mechanisms have been proposed, including a direct effect upon the muscle fibers [20].
2. Total cessation of disabling root pain in 6 of 20 patients suggests that para-spinal administration of botulinum neurotoxin A can help root pain. Only one of these six had distinct muscle spasm in the low back area. The mechanism therefore seems not to be related to reduction of muscle spasm but due to other factors such as anti-pain transmitter/anti-inflammatory effect of Botox or its effect on reduction of muscle volume (transient atrophy) surrounding the irritated or inflamed nerve roots.
3. BoNT-A provided significant pain relief in 6 of 14 patients with failed back surgery. Edwards et al. [6] recently have reported a similar observation in 16 patients.

In conclusion, this study showed long-term (up to 14 months) benefits from BoNT-A treatment in approximately half of the patients with chronic LBP. Treatment was safe, and side effects were few, mild, and transient. Initial responsiveness predicted later responsiveness in over 90% of the patients. Due to high cost, the treating physician should exert fiscal responsibility and evaluate each patient individually for this treatment. Future

studies should investigate benefit and efficacy in subgroups of patients (back strain, osteoarthritis, disc, canal stenosis, etc.), and focus on refinement of injection techniques and on delineation of optimum dose per injection site and per session.

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References

- 1 Karousel-Wood MA, McCune TW, Abdoh A, et al. Predicting work status for patients in an occupational medicine setting who report back pain. *Arch Fam Med* 1994;3:349-55.
- 2 Anderson G. The epidemiology of spinal disorders. In: Frymoyer JW, ed. *The Adult Spine: Principles and Practice*. New York: Raven Press; 1991:107-46.
- 3 Lutz GK, Butzlaff M, Schultz-Venrath U. Looking back on back pain: Trial and error of diagnoses in the 20th century. *Spine* 2003;28:1899-905.
- 4 Foster L, Clapp L, Erickson M, et al. Botulinum toxin A and chronic low back pain. *Neurology* 2001;56:1290-3.
- 5 Lang AM. A pilot study of botulinum toxin type A (botox), administered using a novel injection technique, for the treatment of myofascial pain. *Am J Pain Manag* 2000;10:105-9.
- 6 Edwards K, Dreyer M. Botulinum type A for failed back syndrome. *J Pain* 2004;5(suppl 1):817.
- 7 Tsui JK, Eisen A, Stoessel AJ, et al. Double-blind study of botulinum toxin in spasmodic torticollis. *Lancet* 1986;2:245-7.
- 8 Jankovic J, Schwartz K, Donovan DT. Botulinum toxin injections for cervical dystonia. *Neurology* 1990;40:277-80.
- 9 Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. *Pain* 2004;107:125-33.
- 10 Fillipi GM, Errico P, Santarelli R, et al. Botulinum A toxin effects on rat jaw muscle spindles. *Acta Otolaryngol* 1993;113:400-4.
- 11 Rand MJ, Whaler RC. Impairment of sympathetic transmission by botulinum toxin. *Nature* 1965;206:588-91.
- 12 Ishikawa H, Mitsui Y, Yoshitomi T, et al. Presynaptic effects of botulinum toxin type A on the neuronally evoked response of albino and pigmented rabbit iris sphincter. *Jpn J Ophthalmol* 2000;44:106-9.
- 13 Welch MJ, Purkiss JR, Foster KA. Sensitivity of embryonic rat dorsal root ganglia neurons to Clostridium botulinum neurotoxins. *Toxicon* 2000;38:245-58.
- 14 Wiegand H, Erdman G, Welhoner HH. 125I-labeled botulinum toxin A neurotoxin: Pharmacokinetics in cats after intramuscular injection. *Arch Pharmacol* 1976;292:161-5.
- 15 Harrington JF, Messier AA, Bereiter D, Barnes B, Epstein MH. Herniated lumbar disc material as a source of free glutamate available to affect signals through the dorsal root ganglion. *Spine* 2000;25:929-36.
- 16 McLachlan EM, Janig W, Devor M, et al. Peripheral nerve injury triggers noradrenergic sprouting within dorsal root ganglia. *Nature* 1993;363:543-6.
- 17 Peng B, Wu W, Hou S, et al. The pathogenesis of discogenic low back pain. *J Bone Joint Surg Br* 2005;87:62-7.
- 18 Cheshire WP, Abashian SW, Mann JD. Botulinum toxin in the treatment of myofascial pain syndrome. *Pain* 1994;59:65-9.
- 19 Argoff CE. A focused review on the use of botulinum toxins in neuropathic pain. *Clin J Pain* 2002;18:S177-81.
- 20 Hallett M. How does botulinum toxin work? *Ann Neurol* 2000;48:7-8.