Pain Medicine

Pain Medicine 2010; 11: 1411–1414
Wiley Periodicals, Inc.

Preliminary Research

Botulinum Toxin A for Treatment of Allodynia of Complex Regional Pain Syndrome: A Pilot Study

Delaram Safarpour, MD,* Arash Salardini, MD,† Diana Richardson, MD,*‡ and Bahman Jabbari, MD*

*Department of Neurology, Yale University School of Medicine, New Haven, Connecticut;

†Department of Medicine, University of Florida, Gainesville, Florida

‡West Haven Veterans Administration Hospital, West Haven, Connecticut, USA

Reprint requests to: Delaram Safarpour, 40 Temple Street, 6C Neurology clinic, New Haven, CT 06510, USA. Tel: 203-909-3898; Fax: 203-785-4937; E-mail: delaram.safarpour@yale.edu.

Sponsor: Allergan.

Disclosures
This study was sponsored by Allergan Inc. No governmental or institutional funding.
Dr. Delaram Safarpour reports no disclosures.
Dr. Arash Salardini reports no disclosures.
Dr. Diana Richardson reports no disclosures.
Dr. Bahman Jabbari receives educational and research grants and serves on the advisory board of Allergen Inc.

Abstract

Objective. To investigate the efficacy and tolerability of Botulinum toxin A (BoNT-A) in allodynia of patients with complex regional pain syndrome.

Design. A total of 14 patients were studied. Eight patients were participants of a randomized, prospective, double-blind, placebo-controlled protocol. Six patients were studied prospectively in an open-label protocol. Patients were rated at baseline and at 3 weeks and 2 months after BoNT-A administration. Ratings included brief pain inventory, McGill pain questionnaire, clinical pain impact questionnaire, quantitative skin sensory test, sleep satisfaction scale, and patient global satisfaction scale. BoNT-A was injected intradermally and subcutaneously, five units/site into the allodynic area (total dose 40–200 units).

Results. None of the patients with allodynia showed a significant response after treatment. The treatment was painful and poorly tolerated.

Conclusion. Intrademal and subcutaneous administration of BoNT-A into the allodynic skin of the patients with complex regional pain syndrome (CRPS) failed to improve pain and was poorly tolerated.

Key Words. Complex Regional Pain Syndrome (CRPS); Botulinum toxin; allodynia; Reflex Sympathetic Dystrophy (RSD)

Introduction

Allodynia is an unpleasant clinical condition in which light touch is perceived as pain. It is often associated with hyperesthesia (enhanced sensations). In most cases, the cause is damage to the peripheral nervous system but spinal cord pathology can also cause focal or segmental allodynia (central allodynia).

Over the past two decades, a number of animal studies have shown an analgesic effect for botulinum toxin-A (BoNT-A) after intramuscular and subcutaneous/intradermal administration. Suggested mechanisms from these studies include: decreasing peripheral sensitization through inhibition of pain transmitters (substance P, bradykinin, glutamate, calcitonin gene-related peptide [CGRP]) [1,2] and anti-inflammatory/anti glutamate effect [3,4], decreasing central sensitization through inhibition of muscle spindles discharge [5], and central perception of pain due to the blocking of the retrograde axonal transport [6].

Human, prospective, double-blind, placebo controlled studies report encouraging results. Pain alleviation was noted in patients with low back pain, plantar fasciitis, pelvic pain, migraine; myofascial pain syndrome and allodynic pain associated with trauma, herpes infection and peripheral neuropathy [7–12].

In this communication, we report our experience with BoNT-A in allodynia associated with complex regional pain syndrome (CRPS).

Methods

Fourteen patients meeting the International Association for the study of Pain (ISAP) diagnostic criteria for CRPS [13] were included in this report. Subjects were seen at the neurotoxin treatment clinic of Yale and were treated with BoNT-A. All patients had regions of allodynia in their extremities. Three had additional proximal areas of severe myofascial pain with tender and trigger points in the same side of the affected limb.

Eight of fourteen patients were participants of a double-blind, randomized, prospective, placebo-controlled efficacy/safety study of BoNT-A, which was conducted in 45 patients with focal allodynia (different peripheral etiologies). The other six patients were from an open-label, prospective observations in our clinic. After IRB approval, all study patients signed an informed consent prior to participation. The inclusion criteria consisted of age over 18, severe allodynia associated with CRPS (score > 5), failure to respond to analgesic medications (tricyclic antidepressants, anticonvulsants, opioid analgesics, nonsteroidal anti- inflammatory drugs), pain duration > 3 months and presence of focal allodynia. Exclusion criteria consisted of pregnancy, lactation, neuromuscular junction disorders, axis I diagnosis, prior botox treatment for allodynia and known allergy or sensitivity to botulinum toxins. The area of allodynia was mapped by the patient and by the neurologists on an anatomical sheet. The following rating scales were applied at baseline and at 3 weeks and 2 months botulinum toxin administration:

1. Brief pain inventory (Pain intensity, quality of life)
2. Clinical Pain Impact Questionnaire (PIQ) with focus on pain days
3. McGill pain questionnaire
4. Quantitative sensory test (pressure) using Warner Force Dial instrument
5. Patient Satisfaction scale (very satisfied, somewhat satisfied, neutral, somewhat dissatisfied, very dissatisfied).

The primary outcome in this study was improvement of pain intensity (average and maximum pain) in Brief pain Inventory (50% or more on the scale of 0–10), pain days (past 28 days) in PIQ (30% or more) and improvement of Quantitative sensory skin test. The secondary outcomes, were improvement of activities of daily living in PIQ, improvement of pain severity in McGill scale (mild, moderate, severe) and sleep interference in brief pain inventory. The values were compared with baseline for both botulinum toxin and saline groups at 3 weeks and 2 months, using a two tailed student *t*-test. The six patients of the open-label study were rated by brief pain inventory (0–10), PIQ and patient satisfaction scale at baseline and at 3 weeks and 2 months after BoNT administration.

BoNT-A (Botox, Allergan Inc., Irvine, CA) was prepared by reconstituting vacuum-dried toxin with preservative free 0.9% saline to 50 units/mL concentrations. Prior to injections the skin was sterilled with alcohol. Injections were performed with 1 cc syringe using 27.5 gauge needles. The injections were given as 5 units/site, half intradermally and half subcutaneously over 10–40 sites. The total dose/session ranged from 40 to 200 units (mean: 79.5), depending on the size of the allodynic region. The physician marked the site of injections on an injection diagram. For the saline group, same volume and injection technique was used.

Results

We have stopped enrolling patients in the blinded study and decided to do an interim evaluation of results when eight of nine enrolled (treated) patients (all with CRPS) reported intradermal/subcutaneous injections intolerable, had no pain relief at 3 or 8 weeks and their ratings failed to show any improvements. These patients indicated that even if the injections work, they will not consider this mode of treatment due to extreme level of discomfort.

Five of eight patients were females. The mean age of the group was 47.12 years (37–55) and mean duration of allodynia was 5.5 years (1–20 years). Allodynia affected feet, hands and forearms. At baseline, the mean average pain intensity was 8.25 (range: 7–10) for the BoNT group and 7 (range: 5.1–10) for the saline group ($P > 0.05$). All patients had marked allodynia (>5 to touch in the BPI), trophic skin changes, and local edema (5 of 8). Four patients had history of trauma to the affected limb. Two additional patients had surgery in that limb and one had peripheral neuropathy. Four patients received BoNT and four received placebo. Mean pain days at week 3 and 2 months, were 24.8 ± 6.5 ($P = 0.391$) for the placebo group and 28 for the toxin group ($P > 0.5$). Mean maximum pain intensity for toxin group at 3 weeks and 2 months was 8.5 ± 1.3 ($P = 0.215$) and 8.3 ± 1.3 ($P = 0.182$), respectively. In the placebo group, these values for maximum pain were 8.5 ± 1.3 ($P = 0.215$) and 8.3 ± 1.3 ($P = 0.638$). For average pain, toxin group's mean values at 3 weeks and 2 months were: 7.5 ± 1.9 ($P = 0.215$) and 7.3 ± 1.7 ($P = 0.182$) and the placebo group's values were 7 ± 2.4 ($P > 0.5$) and 6 ± 2 ($P = 0.252$). Secondary outcomes also failed to show improvement. Similar negative results and very poor injection tolerance was observed in six patients who we prospectively followed in the open label trial. In these patients allodynic regions involved dorsum of the hand and forearm.

One of nine patients in the blinded study had post-herpetic neuralgia. This patient reported a positive response regarding to the "pain days interfering with things usually do." These pain days dropped from 28 (at baseline) to 10 and 5 at 3 and 8 weeks. He also reported 90% pain relief at two months (compared with 10%) at baseline ($P < 0.5$). He found injections painful but tolerable.

Discussion

Animal studies of botulinum toxin in allodynia disclosed promising results.

In one study, mechanical allodynia caused by chronic constriction injury of the sciatic nerve, was significantly reduced by injecting BoNT-A (15 picogram/pound) into the mouse's affected paw [14]. In a another study [15], administion of BoNT-A into plantar surface of the rat's left hind paw (10, 20, 30, 40 U/kg) signifcantly reduced the neuropathic pain and allodynia produced by ligating the left L5 and L6 spinal nerves.

Two blinded human studies conducted in healthy volunteers however, reported disappointing results. In one, BoNT-A failed to improve allodynia and reduce neurogenic inflammation caused by capsasin application to the skin [16]. In another study of 15 healthy volunteers with allodynia and hyperalgesia caused by electrical stimulation of the skin, intracutanous injection of BoNT-A (5, 10, 20 mouse units) reduced the size of the flare but failed to alleviate resultant hyperalgesia and allodynia [17]. These results however need to be taken cautiously when relate to pathological allodynia since in disease conditions the pathophysiology may be different from that of capsicin and electrical injury.

Double-blind, prospective studies of BoNT-A in human allodynia, reported encouraging results. In a study of 29 patients with chronic neuropathic pain with allodynia, mostly related to trauma or post-herpetic neuralgia, investigators found signifcant relief of allodynia after intradermal administration of BoNT-A (5 units/site, covering the allodynic region 1.5 cm apart) [12]. In a second study of 20 patients with diabetic neuropathy, injections of BoNT-A into the dorsum of the foot (intrademally, 12 sites, 4 nits/site –50/cc) resulted in significant improvement of allodynia and hyperesthesia [18]. Carroll et al. compared the duration of standard lumbar sympathetic block (LSB) with bupivacaine to LSB with bupivacaine and BoNT-A in nine patients with refractory complex regional pain syndrome. In this study addition of BoNT-A to bupivacaine profoundly prolonged the analgesia from sympathetic block [19].

Our limited blinded study and open-label observations failed to show efficacy of BoNT-A in allodynia associated with CRPS. This outcome may be related to different factors: 1) pathophysiology of allodynia in complex regional pain syndrome is more complex than that of simple trauma, post-herpetic neuralgia and diabetic neuropathy; 2) Our patients had severe CRPS with significant local edema, autonomic changes, fixed painful dystonias. Milder forms of CRPS may render a better response; and 3) our blinded study was limited in scope and a study of a larger number of patients may produce different results. Our poor results and poor patient tolerance in treatment of CRPS's allodynia, may be related to the nature of our cohort (more advanced CRPS) and our method of treatment (intradermal, rather than intramuscular). There are also limitations on unblinded observations such as patient or investigator's bias.

The positive response of our patient with post-herpetic neuralgia is in agreement with the report of other investigators [12]. Argoff [20] reported significant improvement of allodynia and hyperesthesia and the myofascial pain of 11 patients with CRPS in an open-label study. In Argoff's study, BoNT-A was injected into shoulder and periscapular muscles (25–50 U/muscle).

In conclusion, our experience with patients with moderately advanced and advanced, complex regional pain syndrome indicates failure of intradermal and subcutaneous administration of BoNT-A to relieve pain. In these patients, poor tolerance limits the utility of this approach.

This project was supported by a grant from Allergan, Inc. Irvine, CA.

References

1 Hou YP, Zhang YP, Song YF, et al. Botulinum toxin type A inhibits rat pyloric myoelectrical activity and substance P release in vivo. Can J Physiol Pharmacol 2007;85:209–14.

2 Lucioni A, Bales GT, Lotan TL, et al. Botulinum toxin type A inhibits sensory neuropeptide release in rat bladder models of acute injury and chronic inflammation. BJU Int 2008;101:366–70.

3 Cui M, Kanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain 2004;107:125–33.

4 Namazi H. Intravesical botulinum toxin A injections plus hydrodistension can reduce nerve growth factor production and control bladder pain in interstitial cystitis: A molecular mechanism. Urology 2008;72:463–4.

5 Filippi GM, Errico P, Santarelli R, Baqolini B, Manni E. Botulinum A toxin effects on rat jaw muscle spindles. Acta Otolaryngol 1993;113:400–4.

6 Bach-Rojecky L, Lackovic Z. Central origin of the antinociceptive action of botulinum toxin type A. Pharmacol Biochem Bihav 2009;94:234–8.

7 Foster L, Clapp L, Erickson M, Jabbari B. Botulinum toxin A and chronic low back pain: A randomized, double-blind study. Neurology 2001;56:1290–3.

8 Babcock MS, Foster L, Pasquina P, Jabbari B. Treatment of pain attributed to plantar fasciitis with botulinum toxin a: A short-term, randomized, placebo-controlled, double-blind study. Amer Rehab Med 2005;84:649–54.

9 Heidi P, Theresa MS, Sheila AD. Recognizing and treating pelvic pain and pelvic floor dysfunction. Phys Med Rehabil Clin N Am 2007;18:477–96.

10 Joel RS, Ninan TM, Elizabeth WL, Ronald D, Amanda MV. A double-blind, randomized, placebo-controlled comparison of botulinum toxin type a injection sites and doses in the prevention of episodic migraine. Pain Med 2007;8:478–85.

11 Gobel H, Heinze A, Reichel G, Hefter H, Benecke R. Efficacy and safety of a single botulinum type A toxin complex treatment (Dysport) for the relief of upper back myofascial pain syndrome: Results from a randomized double-blind placebo-controlled multicenter study. Pain 2006;125:82–8.

12 Ranoux D, Attal N, Morain F, Bouhassira D. Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain. Ann Neurol 2008;64:274–84.

13 Harden N, Bruehl S, Stanton-Hicks M, Wilson P. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med 2007;8:326–31.

14 Luvisetto S, Marinelli S, Cobianchi S, Pavone F. Antiallodynic efficacy of botulinum neurotoxin A in a model of neuropathic pain. Neuroscience 2007;145:1–4.

15 Park H, Lee Y, Lee J, Park C, Moon DE. The effect of botulinum toxin A on mechanical and cold allodynia in a rat model of neuropathic pain. Can J Anaesth 2006;53:470–7.

16 Schulte-Mattler W, Opatz O, Blersch W, et al. Botulinum toxin A does notalter capsaicin-induced pain perception in human skin. J Neurol Sci 2005;260:38–42.

17 Kramer H, Angerer C, Erbguth F, Schmelz M, Birklein F. Botulinum toxin A reduces neurogenic flare but has almost no effect on pain and hyperalgesia in human skin. J Neurol 2003;250:188–93.

18 Yuan RY, Sheu JJ, Yu JM, et al. Botulinum toxin for diabetic neuropathic pain. Neurology 2009;72: 1473–8.

19 Carroll I, Clark D, Mackey S. Sympathetic block with botulinum toxin to treat complex regional pain syndrome. Ann Neurol 2009;65:348–51.

20 Argoff CE. A focused review on the use of botulinum toxins for the neuropathic pain. Clin J Pain 2002; 18:177–81.