

INTRADERMAL BOTULINUM TOXIN, TYPE A: TO TREAT PAIN DISORDERS

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ABSTRACT

INTRODUCTION: It is known that botulinum toxin, type A, (BoNTA) often has marked effects on pain and headaches. These can occur effects on motor nerve fibers and the mechanism may be an effect on nociceptive sensory afferent or on cholinergic fibers. Intradermal administration was chosen to test this hypothesis for multiple types of painful conditions, on the basis that nociceptive fibers are most numerous in the skin and that cutaneous sensory input contributes to these common painful conditions.

METHOD: 37 patients were selected with a variety of painful conditions (painful neck spasms, CRPS, type 1, diabetic neuropathy, carpal tunnel syndrome, TMD and trigeminal neuralgia). 50 or 100units of intradermal BoNTA was administered. 25 patients had co-existent TMJ symptoms. All headache patients had painful cervical muscle spasms, evidenced by examination. BoNTA was given intradermally by raising a skin wheel at the site of pain on the side of predominant pain symptoms.

RESULTS: All 37 patients had pain reduction with intradermal BoNTA. Neck pain (n=14) was 85% diminished. Back pain (n=7) responded in 2 cases to an extent of 90%. CRPS, type 1, (n=2) resulted in a response of 90%, particularly for the burning symptoms. Diabetic neuropathy (n=2) had an excellent response. Carpal tunnel syndrome (n=1) saw all patients respond. TMJ (n=3) all responded, as did 2 patients with trigeminal neuralgia. Some patients had more than one painful disorder. Average pain reductions across all categories was 85% with average duration of 8.5 weeks (range 3-20). 28 patients (74%) reported virtual eradication of pain, and in particular, that of burning pain. All patients reported relief of painful cervical spasms, even when headache pattern did not change.

CONCLUSIONS: Botulinum toxin, type A, given intradermally, shows a marked ability to reduce painful symptoms in many different pain states, some not studied clinically. It also has excellent efficacy in treating painful cervical spasms. These results compare very favorably, in an earlier than, results from usual intramuscular administration of BoNTA. This open-label data raises many questions about mechanism(s) of action of BoNTA, particularly in the central nervous system, involving uptake into nociceptive fibers and transport to the dorsal horn of the spinal cord. blockade of pain transmission at central facilitative sites may occur, and this, in turn, reduce pain transmission in various pain states. Double-blind studies are definitely warranted to replicate these findings.

RATIONALE

A growing body of preliminary data suggests that BoNTA may have more widespread effects that pharmacologically go beyond its effects on cholinergic motor nerve fibers. Recent studies have shown that BoNTA may block or inhibit release of glutamate, CGRP or Substance P from nociceptive neurons³⁻⁵. These data may explain, in part, the well-known effect of BoNTA to reduce pain longer than its ability to reduce muscular problems/deformities.

We have previously reported initial success in treating headaches of cervical origin with both BoNTA and BoNTB^{4,6}. This study now extends our initial findings with additional data utilizing intradermal BoNTA in other painful states. The index case was a patient with CRPS, type 1, in whom relief of burning pain, swelling and painful radiating symptoms became dramatically better with intradermal BoNTA.

The reason for choosing intradermal BoNTA was twofold: it was reasoned that more nociceptive pain fibers were likely to be found in skin and, as importantly, to avoid giving the toxin into motor cholinergic fibers. In both headache and painful states, it was further reasoned that interference with afferent sensory transmission might contribute to BoNTA's analgesic effects.

METHODS

37 patients with a variety of painful disorders were chosen from a pain and headache practice for treatment with BoNTA. 19 were female and 18 were male. Average age was 51.7 years (range = 24-73) In all cases; patients were being treated with agents to reduce neuropathic pain or with headache prophylaxis medications, or both. These were tapered in most cases where BoNTA had reduced pain severity or frequency. Some patients were treated with 25-50 units of BoNTA; then, it was decided to use a uniform dose of 100 units for each subsequent patient. In all cases, BoNTA was given intradermally. In the case of painful cervical spasm (and headaches), the skin overlying the greater and lesser occipital nerve inlets was injected (see Figure 1). A skin wheel was raised in 2-3 areas in both sites. In the case of diabetic neuropathy and CRPS, type 1, a digit or digits were injected intradermally proximal to the affected area. In the case of TMD, a fixed site injection (see Figure 2) was utilized, as we are studying this disorder in an ongoing manner. Carpal tunnel patients were injected intradermally in the region of the volar aspect of the wrist crease (Figure 3). Trigeminal neuralgia patients were injected intradermally on the affected painful side.

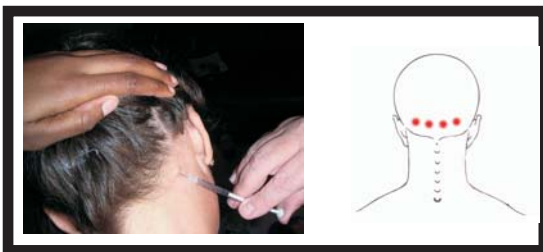


FIGURE 1: OCCIPITAL NERVE INJECTION SITES

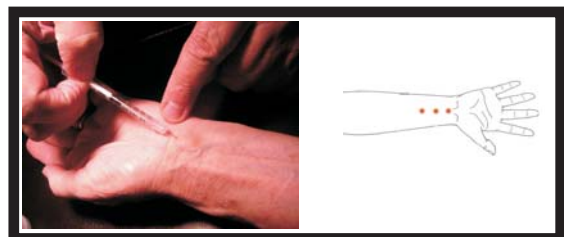


FIGURE 3: CARPAL TUNNEL INJECTION SITES



FIGURE 2: TMJ INJECTION SITES

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CONCLUSIONS:

- INTRADERMAL ADMINISTRATION OF BoNTA IS VERY EFFECTIVE IN TREATING DIVERSE NEUROPATHIC PAIN STATES
- INTRAMUSCULAR ADMINISTRATION AVOIDED IN THIS TECHNIQUE
- STUDY RESULTS BEAR IMPLICATION FOR NEW MECHANISMS OF ACTION OF BoNTA BEYOND EFFECTS ON CHOLINERGIC MOTOR NERVE TERMINALS

RESULTS

In the case of painful cervical spasm, all 14 patients treated with intradermal BoNTA, had reductions in frequency and severity of pain. Average reductions were 85.2% in severity of painful muscle spasm of cervical origin, with an average response time of 9.5 weeks (range 4-21 weeks). In 12 patients with co-existent headaches, there was a 70% reduction in average headache frequency over an average of 8 weeks (range 4-18 weeks). 8 of these patients had prior cervical surgical procedures. 2 of 4 patients treated in the lumbar area responded in terms of reduced back pain. 5 patients with CRPS, type 1, were treated with intradermal BoNTA. All 5 responded with reduced burning and allodynia, as well reduced swelling. 2 cases of diabetic neuropathy were treated with excellent response, although in 1 case re-treatment did not match prior results. Toe dystonia was markedly improved on both occasions. 5 cases of persistent median nerve entrapment pain were treated. 3 had undergone prior nerve release surgery; 2 others did not. All 5 responded with reduction in painful symptoms. 3 cases of temporomandibular disorder (TMD) were also treated with reductions in jaw pain, popping, bruxism, clenching and muscle pain in all 3 treated subjects.

Average pain reductions in responders was 8.5 weeks in duration (range 3-20 weeks), with an average reduction of 68% in pain symptoms across all categories of patients

DISCUSSION

The results presented in this open-label study administering intradermal BoNTA in diverse painful states, suggest an excellent ability of BoNTA to reduce painful symptoms by mechanism(s) other than motor inhibition of muscle contraction. Using this novel administration of the BoNTA, the toxin fragment presumably interrupts ongoing pain signals that promote central sensitization, windup or long-term potentiation in chronic pain and headache states. Whether blockade of glutamate, Substance P, CGRP or other neuromodulators is primarily involved in this process is not known at this time. There is evidence to suggest an interaction of BoNTA with sensory afferents in nociceptive fibers¹, and one open label study with intradermal BoNTB³ treating migraines of cervical origin has shown excellent reductions in migraine headache frequency and severity⁷. A double-blind, placebo-controlled study is being completed at this time. Again, the exact mechanism of BoNTA's effect intradermally is unknown at this time, but double-blind placebo-controlled studies are warranted to explore BoNTA's mechanism(s) of action.

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