The Emerging Use of Botulinum Toxins for the Treatment of Neuropathic Pain

There has been increasing interest in exploring the potential therapeutic benefit of the botulinum toxins in the management of neuropathic pain. Examples of neuropathic pain include painful diabetic polyneuropathy, postherpetic neuralgia (PHN), complex regional pain syndrome, trigeminal neuralgia and neuropathic low back pain. Other chronic pain syndromes may exhibit neuropathic features including migraine and fibromyalgia but are not considered to be typical neuropathic pain states [1–3]. Xiao et al. in this issue of *Pain Medicine* report the results of their randomized controlled study evaluating the effect of subcutaneous injections of botulinum toxin type A (BOTOX) compared with lidocaine and placebo injections for the treatment of PHN [4]. As has been outlined elsewhere in this issue by Xiao et al., BOTOX is known to have analgesic properties with an increasing awareness of proposed mechanisms that underlie these analgesic benefits.

Neuropathic pain is often associated with other chronic pain syndromes, which may be effectively treated with botulinum toxins, in particular, myofascial pain. Allen et al. have demonstrated that 56% of 134 patients with CRPS type 1 demonstrated evidence of myofascial pain in association with their neuropathic pain [5]. This not only confirmed that different types of pain may co-exist within the same patient and that one type of pain, e.g., neuropathic pain may lead to and become associated with another type of pain, but it led to the consideration of how these observations might lead to more effective treatment.

Muscle nociceptors are known to become sensitized by substances including bradykinin and prostaglandins as well as others similar to that seen in neuropathic pain. One investigator has emphasized the role of autonomic nervous system dysfunction in the maintenance and persistence of myofascial pain and has suggested that myofascial trigger points themselves may be caused by a sympathetically maintained pain process [6,7]. In addition, alpha-adrenergic supersensitivity has been observed in patients with sympathetically maintained pain [8]. Looked at together, it would suggest that myofascial pain and dysfunction, through the activation of muscle nociceptors may lead to events that may overlap with those that occur in the development of neuropathic pain. These observations led to a pilot study that was performed with BOTOX to address this potential overlap.

An observational study of 11 patients with CRPS type 1 affecting one upper extremity as well as ipsilateral myofascial pain involving the paracervical, perriscapular and/or suboccipital areas were treated with up to 300 units of BOTOX. The injections were performed into the areas of maximal pain/myofascial dysfunction as assessed during a manual examination. Muscles injected varied from patient to patient and included the sternocleidomastoid, trapezius, splenius capitis, splenius cervicis, and levator scapular, supraspinatus, infraspinatus or rhomboid major muscle groups. Twenty-five to 50 units of BOTOX were injected per muscle. At 6 and 12 weeks following the injection, all patients reported substantial relief not only of their myofascial discomfort but the extremity neuropathic pain complaints and discoloration resolved considerably. Subsequent injections yielded similar results [9].

Jabbari et al. have demonstrated that subcutaneous injections of BOTOX may alleviate burning pain and allodynia in two patients with chronic neuropathic pain associated with spinal cord pathology. Sixteen to 20 injections, five units each were subcutaneously made in painful areas. The visual analog scale score (VAS) was the primary outcome measure used in this study [10]. The authors have concluded that botulinum toxin injections are acting through a nonmotor mechanism of action, hence the ability to achieve results with subcutaneous injections. Gazerani et al. [11] have examined the effects of botulinum toxin type A on capsaicin evoked pain, flare and secondary hyperalgesia in a model of trigeminal nerve sensitization. In this randomized experiment, normal human subjects received either botulinum toxin type A or saline injections prior to capsaicin injection to their forehead. Compared with the saline group, subjects who received botulinum toxin experienced less pain, less of a flare response and less secondary hyperalgesia [11]. Park et al. have demonstrated that in a rat model of neuropathic pain, subcutaneous injections of botulinum toxin type A may reduce both cold and mechanical allodynia [12].

Several reports have suggested that botulinum toxin injections may be helpful in treating PHN. Freund and Schwartz treated seven patients with PHN with subcutaneous injections of botulinum toxin type A at a concentration and dose of 5 units/0.1 mL saline per every 9 cm² of affected skin. No patient received more than 200 units and PHN presentations included trigeminal, thoracic, and lumbar locations. Using VAS scores and results of algometric testing as the two outcome measures, treatment was considered successful with a mean decrease 3 points on the VAS and a clear increase in algometric pressures tolerated by the patients [13]. In a separate more recent report, Liu et al. describe an 80-year-old male with intractable PHN, who responded to botulinum toxin type A injections (duration 52 days). The patient experienced no significant side effects [14].
There have been multiple reports of benefit of botulinum toxin injection for the treatment of trigeminal neuralgia as well as other facial pain syndromes. In an open-label study, Plovessan et al. have injected botulinum toxin into 13 patients with idiopathic trigeminal neuralgia with benefit noted as reduced VAS and a reduction in the surface area of the pain [15]. Turk et al. have described eight patients with trigeminal neuralgia who reported benefit from 100 units of BOTOX into the ipsilateral zygomatic arch in a open label study [16]. Various other case reports as well as other reports of successful treatment of chronic facial pain, all noncontrolled studies are noted as well [17–20]. Witterkinst and colleagues have completed a study of the use of BOTOX in the management of presumed neuropathic pain following neck dissection. In this study, subcutaneous injections of botulinum toxin were successful in reducing neuropathic pain in the neck and shoulder following neck dissections without any serious adverse effects noted. Pain relief was seen by the 28th day following injection [21]. Intracarpal injections of 60 units of BOTOX was shown to reduce pain in patients with “primary” carpal tunnel syndrome in an open label study completed by Tsai and colleagues. While no improvement in electrophysiological studies was noted following injections, a trend in improvement in VAS scores were noted after 3 months in the 5 patients studied. No significant hand weakness or other significant adverse effects were observed [22]. A recent report by Yuan et al. of a pilot study evaluating the use of BOTOX for the treatment of diabetic neuropathic pain suggested that this may be an effective treatment to reduce pain and improve sleep in patients affected by this neuropathic pain condition [23].

Much less work has been reported for the use of botulinum toxin type B in the management of neuropathic pain. Kamen has suggested pain associated with brachial plexopathy may be reduced following botulinum toxin type B injections. Three patients with electrophysiologic and clinical evidence for a brachial plexopathy were treated, under electrophysiologic guidance with botulinum toxin type B with doses ranging from 5,000–7,500 units. The mean decrease in VAS was 2.5. Each of the injected patients requested additional injections 12–16 weeks after the initial injection [24].

In conclusion, while there may be exciting preliminary results available, formal evidence in favor of the use of botulinum toxin for neuropathic pain treatment remains under investigation. Initial data from studies involving neuropathic pain syndromes as diverse as spinal cord injury pain, CRPS, PHN, carpal tunnel syndrome, brachial plexopathy, and trigeminal neuralgia are encouraging but positive large randomized controlled data have been lacking. While the study in patients with PHN by Xiao et al. reported in this issue is the largest randomized controlled study of the use of BOTOX for any neuropathic pain condition and while their results are encouraging multicenter studies are needed to further evaluate the role of BOTOX for treatment of PHN as well as other neuropathic pain conditions. The discovery that botulinum toxin may exert many non-cholinergic actions on the nervous system as well as the known mechanisms of various neuropathic pain states support a potential role of botulinum toxin in the management of neuropathic pain but much more formal clinical data is necessary to better understand the effect of botulinum toxin injections in the treatment of neuropathic pain.

CHARLES ARGOFF, MD
Albany, New York
E-mail: cargoff@nycap.rr.com

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