

POSITION PAPER ON BOTULINUM TOXIN (BOTOX) INJECTION FOR TREATMENT OF CHRONIC MYOFASCIAL PAIN (January 2004)

I. Purpose:

The purpose of this document is to review the available literature concerning the use of Botulinum toxin (Botox) injections for the treatment of chronic myofascial or regional musculoskeletal pain. It is focused to the rationale, outcomes to date, indications, complications, and criteria to be considered for authorization of the study. This information should assist MCOs and providers in authorization decisions for this service.

II. Overview:

Botulinum toxin is a presynaptic neuromuscular blocking agent that when administered causes a temporary clinical denervation of the muscle by blockade of acetylcholine release from the motor nerve terminals. After injection, muscle weakness begins within a week, peaks within two weeks and then plateaus. The plateau is usually prolonged followed by a gradual, slow recovery to baseline as the neuron sprouts new axons and regains the ability to release acetylcholine. The dose administered affects both the duration of the plateau period and the intensity of the denervation. Typically the clinical effects last three to four months post injection.

The FDA has approved two types of botulinum toxins. Botulinum toxin type A (Botox) is FDA approved for the treatment of strabismus, blepharospasm, hemifacial spasm, cervical dystonia, and glabellar wrinkles. Botulinum toxin type B (Myobloc) is FDA-approved for cervical dystonia. For these conditions, the toxins are considered primary treatment with most patients showing improvement lasting three to 5 months when reinjection is usually necessary. Adverse effects are usually limited to weakness to adjacent muscular tissue and are transient. Dosing must be individualized, but higher doses or injection at more frequent intervals have been associated with the patient's development of antibodies that neutralize the toxin's effect. It is estimated that between 3 to 10% of patients treated with Botox develop resistance. The percent of patients who develop resistance to Myobloc is unknown.¹

II. Botulinum Toxin use in Myofascial Pain

In 1994 Cheshire et. al.,² reported on a double-blind, placebo-controlled, cross-over study of injecting either botulinum toxin type A or normal saline into discrete trigger points in the cervical paraspinal or shoulder girdle muscles of six patients with a mean duration of pain of three years. Individuals received either botox or normal saline initially and the opposite injection eight weeks later. Response to the injections was measured every four weeks by change in pain intensity using a visual analog scale (VAS), palpable muscle spasm, muscle tenderness, and verbal pain unpleasantness descriptors. Four of the six patients were found to have a reduction in both pain and muscle spasm following Botox injection but not the saline injection. One individual had no response to either injection and the last individual had a positive response to both injections. Improvement in symptoms was noted for 5-6 weeks. No adverse effects were reported. The study was limited due to small sample size and duration of effect may have been impacted by

small dose size. The authors concluded that a larger study be performed before the treatment could be recommended.

Wheeler³ performed a double-blind study involving 33 patients diagnosed with chronic unilateral neck pain predominantly localized to a unilateral primary trigger point in the cervicothoracic paravertebral muscular region. Patients were assigned to groups to receive 100 Units of Botox, 50 Units of Botox, or placebo. Patients were followed at one week, three week, six week, nine week, three month, and four month intervals with monitoring of readings using a pressure algometer, changes in the Neck Pain and Disability Scale, and patients' subjective assessment of improvement of their symptoms. Clinical improvement for the study was defined as an absence of pain simultaneously on all three measures. Eleven patients received a second injection of 100 Units of Botox in the same site as the first injection and two patients who had previously received Botox received a second injection of 100 Units of Botox in an adjacent symptomatic site four interspaces cephalad and ipsilateral to the first injection. Using the definition of clinical improvement, Wheeler found some improvement in all groups, but no significant improvement between the 50 and 100 Unit Botox injection groups from placebo. He did find significant improvement following the second injection but only 39% of the original sample chose to receive a second injection. He reported no significant adverse events from the injection though two patients had transient ipsilateral arm heaviness and numbness which resolved in the first week and two others noted transient discomfort opposite the injection site. Two others noted a shift in their pain. The authors concluded that follow-up injections of Botox may alleviate trigger point pain and the failure to detect a significant effect from the initial injection may be due to insufficient dosages. Results may have also been impacted by psychosocial factors.

Wheeler et. al.⁴ reported on another double-blind, clinical trial using 50 individuals who had chronic neck pain ranging from 5 months to 39.5 years. Individuals were randomly assigned to receive either a mean dose of 231 Units of Botox (Standard deviation 50 units) or a similar volume of saline in the most painful site of the neck. Clinically significant improvement was measured using a pressure algometer, the Neck Pain and Disability Scale, and the patient's subjective assessment. Individuals were assessed every four weeks for sixteen weeks. For each of the three variables, significant benefits from the injections across time were noted on all of the outcome measures and there was no noted significant improvement from the group receiving Botox. The Botox group did report more adverse events than the normal saline group. The adverse events were excessive weakness of the injected muscle, pain or soreness of the injection site, and flu-like symptoms. They concluded that a single botox injection session without physical therapy is not an effective treatment of chronic neck pain.

Foster et. al.,⁵ tried to determine the efficacy of Botox injections for chronic low back pain. Thirty-one patients with history of low back pain either unilateral or more severe on one side and of greater than six months duration with no findings of acute pathology on MRI were randomly assigned to receive 200 units of Botox or normal saline. Excluded from the study were patients involved in litigation, seeking significant disability, or with evidence of secondary gain. The Botox injection was equally divided among five lumbar sites on the most symptomatic side. Patients were followed at three and eight weeks with monitoring of the Visual Analog Scale and Oswestry Low Back Pain Questionnaire. Clinical response was considered significant with a 50% improvement between the pre and post VAS scores and a two-grade improvement over baseline value in one or more functional subsets of the Oswestry Low Back Pain Questionnaire. Eleven of fifteen patients (73%) receiving Botox showed 50% improvement in their post-injection VAS compared with four of sixteen (25%) in the saline group at three weeks. At eight weeks this had decreased to nine of fifteen patients (60%) receiving Botox and two of sixteen (12.5%) receiving normal saline. For the Oswestry Low Back Pain Questionnaire, ten of fifteen

patients (67%) receiving Botox and three of fourteen (19%) receiving normal saline described improvement. No patient receiving Botox had worsening of pain or function and there were no reported adverse side effects. Those who were seen at six months reported that the analgesic effect lasts three to four months.

A series of articles were published in *The Clinical Journal of Pain* as a Supplement in 2002. The articles described using botulinum toxins to treat a variety of conditions including neuropathic pain,⁶ whiplash-associated disorder,⁷ low back pain,⁸ and myofascial pain.⁹ These articles discuss treatment of the various conditions with botulinum toxins including possible mechanism of action, review of literature, and the author's personal experience. Many of the studies discussed in the articles are from presentations and only a few studies are published in peer journals. Most studies are of small sample size with limited duration (at most two years) of follow-up.

In discussing the use of botulinum toxin to treat neuropathic pain, Argoff⁶ states that it is commonly observed that CRPS patients have concurrent neuropathic pain, autonomic abnormalities, and myofascial symptoms. In the conclusion he indicates that a randomized controlled study is underway and more studies will be necessary.

Freund⁷ described in his article a pilot study injecting fourteen patients with whiplash-associated disorder (neck pain) with 100 units of botulinum toxin A and fourteen other patients with whiplash-associated disorder with normal saline. He found improvement in nine of fourteen receiving botulinum toxin A as assessed by subjective pain, objective ROM of the neck, and subjective function. This improvement lasted less than four months but they responded favorably to reinjection. During the period of functional improvement he recommends patients begin an exercise program aimed at increasing neck ROM and strengthening muscles. Additional studies are underway.

Difazio and Jabbari⁸ state that while Foster et.al.⁵ has published results of a randomized, placebo-controlled study of botulinum toxin A for the treatment of back pain, data presented from other studies have failed to show statistical significance. These studies have been complicated by different designs, different pathologies, and small patient populations. The authors recommend continued study.

A last article by Royal¹⁰ at www.pain.com summarizes the literature regarding the use of botulinum toxin in the treatment of myofascial pain and painful muscle spasm.

III. Benefits/Issues/Recommendations

A. Benefits

Reportedly several studies are underway to determine the efficacy of treating various chronic, neuromuscular disorders with Botulinum toxin type A (Botox) or B (Myobloc). To date, several small studies have indicated an improvement in symptoms and possibly function which lasts approximately three to four months. There is at least one study that questions the efficacy of Botox injection. In general, those responding to injection have focal muscle pain/spasm ideally with "trigger points" that can be injected. Usually the amount of total injection is less than or equal to 200 Units of Botox (type A). Review articles and studies have not identified a significant increase in resistance to injection due to antibody formation. Most articles have described only transient symptoms of nearby muscle weakness/paralysis or local trauma from the injection. There

has been no problems described due to muscle weakness that limits an individuals activity post injection muscles of the neck and trunk.

B. Issues

Based on review of the literature, botulinum toxin type A and type B are being used by a few physicians for treatment of chronic musculoskeletal pain. Studies have been limited in number and at least one study has failed to show a significant improvement over normal saline. Therefore, the procedure must be considered investigational in nature.

Long term outcomes of greater than twelve to eighteen months have not been published. In fact, no study of myofascial, lumbar, or generalized neck pain have described more than two injections with the second injection usually two to three months post the first injection.

Long term adverse effects such as development of antibodies to the toxin or muscle weakness/atrophy have not been described but most individuals to date have had only two series of injections at most.

A cost/benefit analysis has not been performed. The cost of injection of 100 Units of Botox is approximately \$500. A treatment will usually require one or two 100 Unit vials.

C. Recommendations

This treatment is considered investigational at this time.

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¹ Lew, MF: "Review of the FDA-Approved Uses of Botulinum Toxins, Including Data Suggesting Efficacy in Pain Reduction", *The Clinical Journal of Pain* 18:S142-S146, 2002.

² Cheshire, WP, Abashian SW, and Mann JD: "Botulinum toxin in the treatment of myofascial pain syndrome", *Pain* 59:65-69, 1994.

³Wheeler AH, Goolkasian P, and Gretz, SS: “A Randomized, Double-Blind, Prospective Pilot Study of Botulinum Toxin Injection for Refractory, Unilateral, Cervicothoracic, Paraspinal, Myofascial Pain Syndrome”, *Spine* 23:1662-1667, 1998.

⁴ Wheeler AH, Goolhasian P, and Gretz SS: “Botulinum toxin A for the Treatment of Chronic Neck Pain” *Pain* 94:255-260, 2001.

⁵Foster L, Clapp L, Erickson M, and Jabbari B: “Botulinum toxin A and chronic low back pain - A randomized, double-blind study”, *Neurology* 56:1290-1293, 2001.

⁶ Argoff CE: “A Focused Review on the Use of Botulinum Toxins for Neuropathic Pain”, *The Clinical Journal of Pain* 18:S177-S181, 2002.

⁷ Freund BJ, and Schwartz M: “Use of Botulinum Toxin in Chronic Whiplash-Associated Disorder”, *The Clinical Journal of Pain* 18:S163-S168, 2002.

⁸ Difazio M and Jabbari B: “A Focused review of the Use of Botulinum Toxins for Low Back Pain”, *The Clinical Journal of Pain* 18:S155-S162, 2002.

⁹ Smith HS, Audette J, and Royal MA: “Botulinum Toxin in Pain Management of Soft Tissue Syndromes”, *The Clinical Journal of Pain* 18:S147-S154, 2002.

¹⁰ Royal MA, “The Use of Botulinum Toxins in the Management of Myofascial Pain and other Conditions Associated with Painful Muscle Spasm”, www.pain.com