Evidence against Trigger Point Injection Technique for the Treatment of Cervicothoracic Myofascial Pain with Botulinum Toxin Type A

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Background: Traditional strategies for myofascial pain relief provide transient, incomplete, variable, or unpredictable outcomes. Botulinum toxin is itself an analgesic but can also cause sustained muscular relaxation, thereby possibly affording even greater relief than traditional therapies.

Methods: The study goal was to determine whether direct injection of botulinum toxin type A (BoNT-A) into trigger points was efficacious for cervicothoracic myofascial pain, and if so, to determine the presence or absence of a dose–response relation. One hundred thirty-two patients with cervical or shoulder myofascial pain or both and active trigger points were enrolled in a 12-week, randomized, double-blind, placebo-controlled trial. After a 2-week washout period for all medications, patients were injected with either saline or 10, 25, or 50 U BoNT-A into up to five active trigger points. The maximum doses in each experimental group were 0, 50, 125, and 250 U per patient, respectively. Patients subsequently received myofascial release physical therapy and amitriptyline, ibuprofen, and propoxyphene–acetaminophen napsylate. Follow-up visits occurred at 1, 2, 4, 6, 8, and 12 weeks. Outcome measures included visual analog pain scores, pain threshold as measured by pressure algometry, and rescue dose use of propoxyphene–acetaminophen napsylate.

Results: No significant differences occurred between placebo and BoNT-A groups with respect to visual analog pain scores, pressure algometry, and rescue medication.

Conclusions: Injection of BoNT-A directly into trigger points did not improve cervicothoracic myofascial pain. The role of direct injection of trigger points with BoNT-A is discussed in comparison to other injection methodologies in the potential genesis of pain relief.

MYOFASCIAL pain syndrome is a regional skeletal muscular condition presenting with stiffness and pain, characterized by the presence of trigger points in affected musculature. Myofascial trigger points are focal, palpable, hypersensitive taut bands of muscle. Upon palpation, trigger points can produce muscle twitch and referred pain.1,2

Traditional therapeutic approaches for the treatment of myofascial pain have included pharmacotherapy (nonsteroidal antiinflammatory drugs, steroids, tricyclic antidepressants, vasodilators, oral skeletal muscle Relaxants), injection therapy (trigger point injection of local anesthetic with and without corticosteroid, or “dry” needling), physical therapy, and behavioral modification. Long-term benefit with traditional therapy is transient, variable, often incomplete, or nonexistent.3–7 Botulinum toxin type A (BoNT-A) has recently been shown to be analgesic with direct antinociceptive effects in an inflammatory pain model.8 BoNT-A also causes prolonged muscle relaxation by inhibition of acetylcholine release at the neuromuscular junction.9 BoNT-A may offer advantages over traditional modalities, because its effects are sustained and prolonged (3–4 months’ duration).10 Sustained pain relief and muscle relaxation may sufficiently interrupt pain to enable participation in physical rehabilitation, thereby promoting long-term recovery. Furthermore, the efficacy and safety of BoNT-A for the treatment of other disorders with muscle pain (e.g., cervical dystonia, spasticity) is supported by an extensive literature.11–13

The goal of this study was to determine whether injection of BoNT-A directly into trigger points was efficacious in the treatment of cervicothoracic myofascial pain, and if so, to determine the presence or absence of a dose–response relation.

Materials and Methods

This study was approved by the institutions’ respective research review committees (David Geffen School of Medicine at the University of California, Los Angeles, California, and the Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania). All patients gave informed consent. This study was a randomized, double-blind, placebo-controlled, single-injection trial of either saline or 10, 25, or 50 U BoNT-A into each trigger point in patients with cervical or shoulder myofascial pain. Patients were recruited by physician referral. Enrollment in the study was restricted to patients with myofascial trigger points in the surface muscles of the neck and shoulder of at least 6 months’ duration before enrollment. Patients were excluded from the study if they possessed (1) more than five total active trigger points, (2) more than two trigger points in the trapezius.
muscle on any one side of the body, or (3) more than one trigger point in any other single surface muscle on any one side of the body. Other exclusion criteria included (4) pregnancy, (5) age younger than 18 yr, and (6) a history of intolerance to nonsteroidal antiinflammatory drugs.

Two weeks before injection, patients were weaned from all pain medications (nonsteroidal antiinflammatory drugs, antidepressants, muscle relaxants, and opioids). At the time of injection, patients were placed on a standardized tripartite pharmacologic regimen consisting of (1) 10 mg amitriptyline by mouth 2 h before bedtime, increased to 25 mg by mouth 2 h before bedtime after 1 week; subsequently, at 1-week intervals, patients were sequentially increased to 50 mg, followed by 75 mg over the ensuing 2 weeks. If side effects occurred, patients were sequentially reduced to the next lowest dose until side effects disappeared or became tolerable. The regimen also included (2) 800 mg ibuprofen by mouth four times a day (without further titration) and (3) 1 tablet propoxyphene-acetaminophen napsylate by mouth every 4 h as needed for rescue medication. Patients simultaneously received this pharmacotherapeutic regimen and physical therapy focused on myofascial release techniques during the entire duration of the study.

At time of injection using a 22-gauge needle, patients received either placebo (saline) or 10, 25, or 50 U BoNT-A into each trigger point in a particular patient in a randomized, double-blind fashion. (A maximum of five active trigger points were injected per patient. The maximum dose in each experimental group was 0, 50, 125, and 250 U per patient, respectively.) Designation of a trigger point as “active” signified reproduction of the patient’s pain complaint upon palpation of the trigger point and elimination of the pain with inactivation of the trigger point by acupuncture. A randomization table was designed, and syringes for injection were prepared by an individual who was not involved in the study. The total volume of each injectate was controlled at 0.5 ml per trigger point.

Outcome measures included (1) visual analog pain scale (VAS) score “over the last 24 h,” (2) use of propoxyphene-acetaminophen napsylate as rescue medication, (3) pain threshold as measured by pressure algometry,15–17 and (4) the 36-Item Short-Form Health Survey (SF-36) as a quality-of-life measure.18,19 Patients kept a daily log of VAS scores (first time point was before injection) and use of rescue medication for the first 8 weeks of the study. Patients were asked to assess their pain over the last 24 h using the VAS at the same time each day. Logs were returned to investigators at follow-up interviews at 1, 2, 4, 6, 8, and 12 weeks after injection. Patients completed another VAS assessing pain over the last 24 h at the 12-week postinjection interview. Pressure algometry was performed to determine pain threshold, and patients completed the SF-36 before injection and at the previously mentioned follow-up interview time points. To repetitively perform algometry over the same areas of skin, a single dot of methylene blue was placed over each trigger point at the time of injection and at each follow-up interview. The sites of injection were also marked on anatomical charts. Triplicate measurements (kg/cm²) were obtained for pressure algometry, and a mean threshold was determined for each trigger point.

Statistical Analysis

Demographic data were compared using chi-square analysis with Fisher exact test for nonparametric data and Student t test and analysis of variance for parametric data. The daily VAS scores and rescue medication use were analyzed using the area under the curve of the differences from baseline (also known as Sum of Pain Intensity Differences). Analysis of variance was used to compare the areas under the curves. Two separate intergroup analyses were performed. In the first, placebo was compared to individual BoNT-A dosages. In the second analysis, placebo was compared to the combined data from all BoNT-A dosages. VAS scores obtained at weekly intervals (1–8 weeks) and week 12 were analyzed by repeated-measures analysis of variance. Pressure threshold algometry was analyzed using repeated-measures analysis of variance. SF-36 data over 12 weeks for each subscale were analyzed using generalized estimation equation regression models that adjusted for multiple values per patient. The overall models contained age, sex, day, day squared, baseline level, and BoNT-A dose as independent variables. For each subscale of the SF-36, three separate intergroup analyses were performed. In the first, placebo was compared to all BoNT-A dosages. In the second, placebo and 10 U were compared with 25 U and 50 U. In the third, placebo, 10 U, and 25 U were compared with 50 U.

Unless otherwise indicated, the mean ± SD was reported as the measure of central tendency for parametric data. The median with range was reported as the measure of central tendency for ordinal data. A P value of 0.05 or less was chosen to indicate statistical significance.

Results

Demographic data for all dosage groups are presented in table 1. There was no difference among the placebo group and the three treatment groups at baseline with respect to age, sex, history of work injury, number of workers compensation cases, number of trigger points, or VAS score.

The results of the VAS Sum of Pain Intensity Differences analysis (table 2), analysis of mean weekly VAS
scores (table 3), comparison of rescue dosing among groups (table 4), and analysis of mean trigger point pain threshold by algometry (table 5) revealed no difference among the placebo group and the three treatment groups for each of the respective outcome measures. However, all four groups showed a time effect for each of the respective outcome measures. All treatment groups, including placebo, showed a significant improvement in VAS scores, use of rescue medication, and trigger point pain threshold by algometry over the course of the study ($P < 0.001$), with no observed differences among treatment groups.

For the SF-36, BoNT-A-treated patients demonstrated improvement in the Role Emotional subscale of the SF-36 as compared with placebo ($P < 0.05$). A trend toward improvement was seen in the Vitality ($P = 0.053$) and Social Functioning ($P = 0.057$) subscales. A dose-response effect was not demonstrated for any subscale.

Three patients who received BoNT-A experienced flu-like symptoms that were transient and resolved during the course of the study. No other adverse events occurred.

**Discussion**

The results of this study suggest that injection of BoNT-A directly into trigger points does not improve pain in patients with cervicothoracic myofascial pain syndrome. No significant differences were found between placebo and BoNT-A groups with respect to pain, pain threshold, or use of rescue medication. Do the findings of this study suggest a general lack of effectiveness of BoNT-A in the treatment of cervicothoracic myofascial pain or, rather, lack of efficacy with the methodology of direct trigger point injection?

It is almost intuitive for an anesthesiologist to consider directly injecting BoNT-A into trigger points, given our long-standing experience with trigger point injection of local anesthetic with and without corticosteroid. Given the neuromodulatory antinociceptive effects of BoNT-A, direct injection of trigger points would seem appropriate because they are the area of most intense pain. It has long been known that BoNT-A inhibits acetylcholine release at the neuromuscular junction (see below) by cleavage of the plasma membrane bound peptide, SNAP-25, preventing vesicle-dependent neurotransmitter release.

An identical mechanism for inhibition of vesicle-dependent neurotransmitter release has been demonstrated for several neurotransmitters (substance P, vasoactive intestinal polypeptide, calcitonin gene-related peptide, glutamate). Therefore, injection of BoNT-A into trigger points (as the area of most intense pain) would seem mechanistically warranted to decrease local neurotransmitter release, reduce neuropathic inflammation, and cause pain relief (direct analgesic effect). However, the results of this study suggest that direct injection of BoNT-A into trigger points does not improve pain in patients with cervicothoracic myofascial pain syndrome.

As mentioned, BoNT-A can also cause sustained and...
prolonged muscle relaxation by inhibition of acetylcholine release at the neuromuscular junction. A hypothesized primary dysfunction in the causation of trigger points and myofascial pain syndrome is an increased release of acetylcholine from the neuromuscular junction after chronic overload or stretching of muscle. According to this hypothesis, trigger points are located exclusively in the motor endplate zone. Chronic postjunctional membrane depolarization could cause continuous release and inadequate uptake of calcium ions from the sarcoplasmatic reticulum, resulting in continuous sarcomere contraction and increasing demand for energy. At the same time, sustained muscle fiber contraction would lead to local ischemia via compression of blood vessels and reduced nutrition, oxygenation, and fatigue. This would result in nociceptor sensitization via the process of neurogenic inflammation and subsequent release of excitatory amino acids and neuropeptides, causing more acetylcholine release and a vicious cycle (the integrated trigger point hypothesis). Development of postural abnormalities perpetuates dysfunction and pain. BoNT-A causes inhibition of acetylcholine release at the neuromuscular junction, resulting in sustained muscle relaxation and potential reversal of the aberrant pathophysiology. However, the results of this study suggest that direct injection of BoNT-A into trigger points does not improve pain in patients with cervicothoracic myofascial pain syndrome.

Evidence suggests that BoNT-A can potentially generate pain reduction by other processes besides chemodenervation. BoNT-A may reduceafferent nociceptive transmission to the central nervous system by normalization of sensitized neuromuscular spindle activity.

Other studies demonstrate retrograde uptake of BoNT-A into the central nervous system via axonal transport after intramuscular injection, suggesting the potential for a direct central effect.

Given this theoretical framework for the potential analgesic effects of BoNT-A, we could infer that BoNT-A would be effective therapy for any painful condition dependent on relaxation. The results of previous studies are conflicting with respect to the efficacy of direct injection of BoNT-A into trigger points in the treatment of cervicothoracic myofascial pain. Early studies examining the role of direct trigger point injection with BoNT-A for cervicothoracic myofascial pain involved too small a number of patients to be deemed more than probes (n = 6 and n = 2, respectively). Alo et al. performed an uncontrolled, open-label study that suggested efficacy for bolus injection. Freund and Schwartz performed a double-blind, randomized, placebo-controlled trial of direct trigger point injection in patients with chronic whiplash injuries, showing reduction in pain and improved cervical range of motion. Wheeler et al. performed two double-blind, randomized, placebo-controlled trials of direct trigger point injection without positive results after a single injection session. Lang performed an uncontrolled, open-label...
study using grid-pattern midbelly injection of BoNT-A (rather than direct trigger point injection) with positive therapeutic effects. The results of the present study suggest that injection of BoNT-A into trigger points does not improve pain in patients with cervicothoracic myofascial pain syndrome who simultaneously receive physical therapy and pharmacotherapy.

Let us examine the potential role of injection methodology in explaining these disparate results. There are several potential injection techniques for administration of BoNT-A besides trigger point injection. (1) Given the chemodenervation effect of BoNT-A, injections could be electromyographically directed toward the motor end plate zone, because this is the only part of the muscle containing motor nerve terminals.31,32 (2) Compartment technique is an intramuscular bolus anywhere within the body of the muscle. It is usually reserved for deep muscles that are difficult to localize (e.g., psoas, piriformis), requires imaging, and relies on diffusion of BoNT-A to produce relaxation.20,33 (3) Multiple injection sites within single muscles have also been used to enhance spread and facilitate relaxation.34 There is some evidence that multiple injection techniques within a single muscle are superior to single injection with respect to pain in cervical dystonia.35 (4) In an open-label study, BoNT-A has been injected in a grid-like fashion (without electromyography) throughout the midbelly of affected muscles rather than exclusively at trigger points.36 Mechanistically, midbelly injection could also yield superior chemodenervation and relaxation.

BoNT-A may be conceptualized as producing chemodenervation within a "sphere" of diffusion, because toxin diffuses in all directions from an injection site.35 The size of the "sphere" of chemodenervation is determined by the pharmacologic parameters of dose and volume.31 Ideally, BoNT-A should be directed toward the motor endplate zone to produce optimal chemodenervation at the neuromuscular junction. Unfortunately, these zones are not known for most muscles (including the cervicothoracic musculature). In an experimental model using the rat tibialis anterior muscle, injection of BoNT-A at a distance of 0.5 cm from the motor endplate zone resulted in a 50% decrease in paralysis.31 Therefore, location of injection may be important in the efficacy of BoNT-A, but compensation could be obtained by adjustment of dose or volume of injectate or both. Inexact knowledge of motor endplate zones could be compensated by midbelly injection, given that extrafusal muscle fibers are generally innervated in a circumscribed area at their midbelly.36

Again, it is almost intuitive for an anesthesiologist to consider directly injecting BoNT-A into trigger points, which is why we chose this injection methodology. However, dogmatic injection of trigger points without analysis of the postural relations of the cervicothoracic musculature may ignore biomechanical functional relations (table 6 and fig. 1). For example, if the splenius capitis and semispinalis capitis (neck extensors) were weakened by BoNT-A in a patient with the postural abnormality of propulsion (fig. 1), the scalenes, pectoral muscles, and sternocleidomastoid muscles could flex the neck further. Weakening neck flexors without simultaneously weakening neck extensors in a patient with propulsion could enhance the postural abnormality and perhaps actually increase pain. The postural abnormality of propulsion is common in patients with cervicothoracic myofascial pain. This study chose to purposefully ignore the presence of postural abnormalities and the functional relations of the cervicothoracic musculature, recapitulating the injection methodology of trigger points with local anesthetic. To date, no study of the use

### Table 5. Trigger Point Pain Threshold by Pressure Algometry

<table>
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<tr>
<th></th>
<th>Placebo (n = 35)</th>
<th>10 U/TP BoNT-A (n = 32)</th>
<th>25 U/TP BoNT-A (n = 34)</th>
<th>50 U/TP BoNT-A (n = 31)</th>
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<tbody>
<tr>
<td>Week 0</td>
<td>4.4 ± 1.6</td>
<td>4.2 ± 1.4</td>
<td>4.1 ± 1.7</td>
<td>4.2 ± 1.6</td>
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<tr>
<td>Week 1</td>
<td>5.3 ± 2.3</td>
<td>4.4 ± 1.8</td>
<td>4.1 ± 2.1</td>
<td>4.2 ± 1.6</td>
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<tr>
<td>Week 2</td>
<td>5.4 ± 2.0</td>
<td>4.6 ± 2.0</td>
<td>4.4 ± 2.6</td>
<td>4.5 ± 1.6</td>
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<tr>
<td>Week 3</td>
<td>5.7 ± 2.4</td>
<td>5.1 ± 2.8</td>
<td>4.7 ± 2.7</td>
<td>4.6 ± 1.8</td>
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<tr>
<td>Week 4</td>
<td>5.9 ± 2.7</td>
<td>5.4 ± 2.6</td>
<td>4.9 ± 2.3</td>
<td>5.1 ± 1.8</td>
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<tr>
<td>Week 6</td>
<td>5.9 ± 2.7</td>
<td>5.0 ± 1.9</td>
<td>5.2 ± 2.2</td>
<td>6.0 ± 3.6</td>
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<tr>
<td>Week 8</td>
<td>5.8 ± 2.3</td>
<td>5.4 ± 2.9</td>
<td>5.2 ± 2.0</td>
<td>6.5 ± 3.9</td>
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<tr>
<td>Week 12</td>
<td>6.8 ± 3.4</td>
<td>5.3 ± 3.1</td>
<td>5.7 ± 2.6</td>
<td>6.3 ± 3.8</td>
</tr>
</tbody>
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Data are presented as mean (kg/cm²) ± SD. Analysis of variance (repeated measures): dosage effect: P = 0.61; time effect: P < 0.001; dose × time effect: P = 0.61.

BoNT-A = botulinum toxin type A; TP = trigger point.

### Table 6. Function of Cervicothoracic Muscles

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<tr>
<th></th>
<th>Levator scapulae</th>
<th>Spleen capitis and cervicis</th>
<th>Sternocleidomastoid</th>
<th>Pectoralis minor and major</th>
<th>Sternocleidomastoid</th>
<th>Splenius capitis and cervicis</th>
<th>Semispinalis capitis</th>
<th>Trapezius</th>
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<tbody>
<tr>
<td>Shoulder elevation</td>
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<td></td>
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<td>Head rotation</td>
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<td>Neck flexion</td>
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<td>Neck extension</td>
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<td>Head tilt</td>
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of BoNT-A in myofascial pain has cataloged, examined, or accounted for the presence or absence of postural abnormalities with respect to the methodology of injection.\textsuperscript{5,7,26–30}

Long-term benefits from traditional therapies for myofascial pain are transient, variable, often incomplete, or nonexistent.\textsuperscript{3–7} However, unlike the current study, no previous study of BoNT-A in myofascial pain has controlled for the concomitant use of both pharmacotherapy and physical therapy.\textsuperscript{5,7,26–30} Lack of control of pharmacotherapy and physical therapy confounds the interpretation of the results of previous studies. There was a clear time effect on all outcome variables independent of treatment groups (no significant dose × time effect interaction) in the current study, suggesting that the simultaneous use of pharmacotherapy and physical therapy was able to bring some relief. It should be noted that although there is some evidence that the modalities used during physical therapy may be efficacious in treating cervicothoracic myofascial pain,\textsuperscript{3–5} there is no evidence that amitriptyline or other antidepressants are effective.\textsuperscript{37} It should also be noted that supplementation of “standard” pharmacotherapy and physical therapy by injection of BoNT-A provided no additional benefit in the current study. The use of BoNT-A in myofascial pain would not be clinically advantageous if this and future studies were unable to demonstrate a clear superiority over conventional therapies.

Despite the lack of a difference in pain relief between placebo and BoNT-A groups, BoNT-A–treated patients demonstrated improved or a trend toward improvement in three subscales of the SF-36 as compared with placebo. The rationale for improved health-related quality of life scores without improvement in pain relief in the current study is obscure and may simply represent type I error.

In conclusion, this study suggests that injection of BoNT-A directly into trigger points does not improve pain relief in patients with cervicothoracic myofascial pain syndrome. Future studies should carefully address the effects of dosing, volume, postural abnormalities, choice of muscles to inject, injection site, and injection technique in the use of BoNT-A for cervicothoracic myofascial pain syndrome.

The authors thank Amy Lang, M.D. (Volunteer Assistant Professor, Department of Rehabilitation Medicine, Emory University School of Medicine and Hospitals, Lawrenceville, Georgia), for providing the figure of a patient with propulsion.

References


Fig. 1. This patient exhibits the postural abnormality of propulsion with shortened cervical paraspinal muscles, elevated and internal rotation of the shoulder girdles (rounding).

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