Botulinum toxin type A for the treatment of head and neck chronic myofascial pain syndrome

A systematic review and meta-analysis

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ABSTRACT

Background. The authors conducted a systematic review to study the efficacy of botulinum toxin type A (BoTN-A) in the treatment of myofascial pain syndrome.

Types of Studies Reviewed. The authors identified randomized, double-masked, placebo-controlled studies on June 1, 2016, from PubMed, Web of Science, and the Cochrane Library. Three of the authors assessed the studies for risk of bias. Outcomes included pain reduction on a visual analog scale, the number of responders, and the posttreatment pain threshold to applied pressure using algometry.

Results. The initial search strategy yielded 253 unduplicated references, which the authors reduced to 13 relevant studies. The authors included 11 studies in the meta-analyses as the investigators of those studies had reported similar outcomes. Pooled results showed a nonsignificant improvement in the posttreatment intensity of pain in the BoTN-A group compared with the placebo group at 4 to 6 weeks (standardized difference in means [SDM], –0.110; 95% confidence interval [CI], –0.344 to 0.124; $P = .356$) and a significant improvement at 2 to 6 months (SDM, –0.360; 95% CI, –0.623 to –0.096; $P = .008$). The number of study participants who responded to treatment was not statistically significantly different between the groups (risk ratio, 1.346; 95% CI, 0.922-1.964; $P = .123$) nor was the increase of pain threshold to pressure (algometry) at 2 months (SDM, 0.131; 95% CI, –0.178 to 0.440; $P = .405$). The study investigators reported no major adverse events.

Conclusions and Practical Implications. Pain was reduced significantly in the group that received BoTN-A compared with the placebo group at 2 to 6 months but not at 4 to 6 weeks (with moderate quality of the evidence). Additional studies with larger numbers of participants are needed to confirm these results.

Key Words. Myofascial pain; myofascial trigger points; botulinum toxin type A; visual analog scale; randomized controlled trials; meta-analysis.
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Myofascial pain syndrome (MPS) is a significant health problem affecting 85% of the general population at some period in their lifetime with an overall prevalence of approximately 46%.[1,2] Patients with MPS usually experience pain, mood changes, various levels of physical disability, and an overall lower quality of life.[3] This syndrome is characterized by having myofascial trigger points (MTrP) located in contracted knots associated with tense muscle fibers; these tense muscle fibers extend to the muscle attachment called taut bands.[4] MTrPs usually feel stiff and provoke pain when palpated. Microscopic examination of MTrPs reveals hypercontracted muscle fibers associated with sustained calcium release within the sarcoplasmic reticulum caused by continuous generation of action potential owing to intense neural activity.[5] Investigators have associated these

Supplemental material is available online.

pathological findings, linked to constant muscular hypercontraction activity, with the depletion of adenosine triphosphate and metabolic stress.[6]

After identifying a patient's trigger points by means of clinical palpation and an assessment of the patient's symptoms, the practitioner can choose from a variety of treatment options, including occlusal appliance, massage therapy, physical therapy, acupuncture, heat or cold pads, and avoidance of triggers.[7] One therapy being studied is the injection of botulinum toxin type A (BoTN-A) into the area of the trigger point. The number of trigger points injected, as well as the number of injections per trigger point, varies from study to study. BoTN-A is a polypeptide protoxin produced by clostridium botulinum bacteria. This protoxin inhibits the release of acetylcholine (ACh) from the presynaptic nerve membrane; the release of ACh is necessary for generating activity at the neuromuscular junction.[8] BoTN-A inhibits the ACh exocytosis in the cholinergic nerve endings; it cleaves synaptosome associated protein 25, which is needed for docking the ACh vesicle to the presynaptic membrane. Without docking, the vesicles will not release ACh into the synaptic cleft, resulting in paralysis of the innervated structure.[9]

Paralysis occurs within 6 hours of administration, and clinical effects will be apparent within 24 to 72 hours. The body overcomes the botulinum blockade of the neuromuscular junction by sprouting out presynaptic axons from blocked muscle terminals. This recovery usually happens within 90 days, however, repeated applications of BoTN-A will increase this period.[10] The results of a 2015 study[11] showed that BoTN-A also inhibits the release of various nociceptive mediators such as substance P, calcitonin gene–related peptide, and glutamate. These results explain why, in many cases, pain relief occurs considerably before any decrease in muscle activity is noted.[11]

In 1994, investigators[12] reported the results of the first clinical trial related to the treatment of MPS with BoTN-A. The effectiveness of this treatment modality has not been well established because the lack of standardization, the different doses, and the different outcomes that investigators of subsequent studies used have generated mixed results. We designed this review to analyze the randomized controlled trials (RCTs) regarding the efficacy of BoTN-A injection at active trigger points as a treatment for MPS, as well as the antinociceptive effects of BoTN-A as outlined by the investigators of various studies.

METHODS

Inclusion and exclusion criteria. We limited included studies to RCTs related to the efficacy of providing BoTN-A for head or neck trigger point injections compared with providing placebo (that is, normal saline solution). The investigators of the included studies conducted their research with patients who had MPS, and the investigators of the RCTs needed to have reported at least 1 clinical end point. We excluded case reports, case series, clinical trials that were not randomized, editorials, letters to the editor, literature and systematic reviews, animal studies, and clinical guidelines. We cross-referenced reviews to identify all relevant trials. Three calibrated reviewers (M.K., K.M., N.V.) individually assessed eligible studies to determine inclusion or exclusion. These reviewers omitted articles not available in the English language.

Search methods for identification of studies. We searched the following 3 electronic databases:

- MEDLINE via PubMed (searched on March 12, 2015, and updated June 1, 2016) limited to English and humans: ("Botulinum Toxins"[Medical Subject Headings {MeSH}]) OR (Botulinum Toxins Type A) OR Botox OR (Clostridium botulinum A Toxin) OR (Botulinum Neurotoxin A) OR (Clostridium Botulinum Toxin Type A) OR (OnabotulinumtoxinA) OR BTX) AND ("Myofascial Pain Syndromes"[MeSH] OR Trigger point injection).
- The Web of Science (searched on March 12, 2015, and updated June 1, 2016): *TOPIC: (Botulinum Toxin* OR Botulinum Toxin* Type A OR Botox OR Clostridium botulinum A Toxin OR Botulinum Neurotoxin A OR Clostridium Botulinum Toxin Type A OR OnabotulinumtoxinA OR BTX-A) AND TOPIC: (Myofascial Pain Syndrome* OR Trigger point injection).*
- The Cochrane Library (searched on March 12, 2015, and updated June 1, 2016): (Botulinum Toxin*) OR (Botulinum Toxin* Type A) OR Botox OR (Clostridium botulinum A Toxin) OR (Botulinum Neurotoxin A) OR (Clostridium Botulinum Toxin Type A) OR (OnabotulinumtoxinA) OR BTX-A) AND (Myofascial Pain Syndrome* OR Trigger point injection).

Data collection and analysis. ***Selection of studies.*** Three reviewers (M.K., K.M., N.V.) independently screened titles and abstracts of the articles identified by the search strategy to assess inclusion and exclusion criteria. They obtained the full-text articles associated with those titles and abstracts that fulfilled the inclusion criteria (for example, RCTs for which the investigators had used BoTN-A with an intervention group and a placebo for a comparison group) and for those studies for which they could not make a decision regarding inclusion or exclusion solely on the basis of the abstract

ABBREVIATION KEY. **ACh:** Acetylcholine. **AE:** Adverse event. **BoTN-A:** Botulinum toxin type A. **GRADE:** Grading of Recommendations, Assessment, Development and Evaluation. **MeSH:** Medical Subject Headings. **MPS:** Myofascial pain syndrome. **MTrP:** Myofascial trigger points. **NSAID:** Nonsteroidal anti-inflammatory drug. **RCT:** Randomized controlled trial. **RDC/TMD:** Research Diagnostic Criteria for Temporomandibular Disorders. **TMD:** Temporomandibular disorders. **TMJ:** Temporomandibular joint. **VAS:** Visual analog scale.