Review of the Use of Botulinum Toxin in the Setting of Back Pain

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Abstract The current understanding of the pathophysiology of myofascial pain and the mechanism of botulinum neurotoxin (BoNT) suggest that BoNT may be well suited to the treatment of back pain. The few randomized controlled trials that have been done to evaluate the efficacy of BoNT in the treatment of myofascial low back pain have shown some promising results. Results from the more numerous trials of BoNT for treatment of myofascial thoracic and neck pain have only shown trends toward the efficacy of BoNT treatments compared with control treatments.

Keywords Botulinum toxin · Botox · Low back pain · Neck pain · Myofascial pain

Introduction

Back pain is associated with a significant socioeconomic and health impact. Health care expenditure for back pain in the USA was estimated at \$90.7 billion in 1998 [1]. The annual prevalence of low back pain ranges from 15 to 45 %. The resulting loss of productivity is evidenced by an average of nine workdays missed per year in the USA for individuals with back pain [2]. The incidence of neck pain

over a 1-year period ranged from 27.1 % in Norway to 47.8 % in Quebec, Canada. Between 11 and 14 % of workers were limited in their activities because of neck pain [3]. In 1990 there were almost 15 million visits to physicians' offices for "mechanical" low back pain [4]. Opioids are a common form of medical treatment for back pain. The mean annual prescription medication cost is eight times higher for opioid abusers versus nonabusers, \$15,884 versus \$1,830 [5]. The treatment and productivity costs associated with back pain have continued to rise despite an ongoing effort to describe the pathophysiology of different types of back pain and identify treatments with significant and lasting benefit.

Myofascial pain is defined as pain that originates from trigger points, taught bands of muscle that reproduce pain patterns on palpation. Myofascial pain can be present with or without other pain generators and often causes referred pain to the surrounding muscles. The cause of myofascial pain is controversial, but studies have elucidated at least part of the pathophysiological mechanism involved. Pertinent to this review are the findings of a pathological increase in the release of acetylcholine (ACh) by the nerve terminal evidenced in electrodiagnostic studies of the affected resting muscle [6•]. A positive-feedback loop has been proposed to explain the persistence of increased ACh release by involved trigger points. In the proposed feedback loop, local ischemia and increased metabolism are caused by sustained sarcomere contraction leading to energy crisis of the tissue. Release of sensitizing substances then generates pain and propagates increased ACh release [6•]. Botulinum neurotoxin (BoNT) inhibits the release of ACh from the nerve terminal and so theoretically should be able to interfere with the proposed positive-feedback loop.

BoNT has been investigated in the treatment of back pain, muscle disorders, and headaches. It has been shown to be effective in the treatment of cervical dystonia by

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relieving both muscle spasticity and pain [7]. The mechanism of BoNT has been well demonstrated as muscle relaxation, but studies also suggest a separate analgesic mechanism through inhibition of the release of substance P [8]. The following is a review of the literature on the efficacy of BoNT in the treatment of back pain.

Literature Search

The electronic literature was searched using the keywords “botulinum toxin,” “Botox,” “low back pain,” “neck pain,” and “myofascial pain” in the PubMed database.

Additional studies were included after reviewing the bibliographies of relevant articles. Studies were excluded from this review if they were not randomized controlled trials (RCTs) comparing BoNT with alternative treatments or if they included subjects with fibromyalgia or subjects with pain generators other than myofascial pain. The literature was searched up to February 1, 2013.

Low Back Pain

Few RCTs of intramuscular injections of BoNT for the treatment of low back pain have been performed (Table 1).

Table 1 Summary of randomized controlled trials of intramuscular injections of botulinum neurotoxin (BoNT) for the treatment of low back pain

Study	Methods	Participants	Interventions	Outcomes
De Andres et al. [9•]	N: 28 Dropouts: 1 RCT Double blind	Chronic low back pain with bilateral trigger points and duration longer than 6 months	For each participant, 50 U BoNT-A was administered to affected muscles on one side and either 0.9 % NaCl or 0.25 % bupivacaine was administered to muscles on the other side. Randomization was performed both for the side into which BoNT was injected and for the opposite side, for which control injectant was used. Overall, BoNT was injected into 88 muscles, including psoas (18.5 %), quadratus lumborum (18.5 %), and psoas and quadratus lumborum (63 %)	Evaluation by the VAS at 15, 30, and 90 days after treatment. No statistically significant difference
Fishman et al. [10•]	N: 87 Dropouts: 20 RCT Double blind 3 groups	Sciatica diagnosed by physical examination and electromyogram	All groups received standard physical therapy twice weekly for 12 weeks. Both groups received injections of 20 mg triamcinolone and 2 % lidocaine into the piriformis muscle. The trial group also received 300 U BoNT-A	VAS evaluation reported every 2 weeks for 12 weeks. Patients with 50 % or more improvement on the VAS at their last 2 visits: 65 % (13/21) of patients treated with BoNT; 32 % (10/31) of patients treated with triamcinolone/lidocaine; 6 % (1/15) of patients treated with placebo. Statistically significant difference
Foster et al. [11•]	N: 31 Dropouts: 3 RCT Double blind 2 groups	Lateralizing low back pain between L1 and S1 lasting more than 6 months	Participants were randomized to receive either 200 U BoNT (40 U per site) or saline injections of identical volumes into L1–L5 paravertebral muscles on the more painful side. BoNT was injected into L2–S1 paravertebral muscles if pain extended to the sacral area	VAS and OLBPG were evaluated for more than 50 % pain reduction after the procedure: at 3 weeks, 73.3 % (11/15) of the BoNT group and 25 % (4/16) of the saline group; at 8 weeks, 66.7 % (10/15) of the BoNT group and 18.8 % (3/16) of the saline group. Statistically significant difference

OLBPQ Oswestry Low Back Pain Questionnaire, RCT randomized controlled trial, VAS visual analog scale

The subjects included in these three studies had low back pain or symptoms of sciatica for over 6 months. The acute and subacute low back pain populations were not represented in these studies.

The studies of Foster et al. [11•] and De Andres et al. [9•] enrolled patients with myofascial low back pain. These two studies targeted different muscles with the BoNT injections, paraspinal muscles in one study and quadratus lumborum and psoas muscles in the other study. Similar doses of BoNT were used in the two studies. The subjects in the study of Fishman et al. [10•] had symptoms of sciatica and piriformis syndrome; the piriformis muscle was therefore targeted for BoNT injections. Although De Andres et al. [9•] performed injections bilaterally, BoNT was only injected unilaterally in the study of Fishman et al. Similarly, Foster et al. [11•] injected BoNT unilaterally, but there was no intervention on the contralateral side.

Fishman et al. [10•] and Foster et al. [11•] both found a statistically significant reduction in pain on a visual analog scale (VAS) when compared with the control groups. De Andres et al. [9•] did not find a statistically significant reduction in back pain as measured by the VAS reported for the BoNT-treated side the versus saline-treated side.

Thoracic and Neck Pain

The studies included in Table 2 are all RCTs, but their power, methods, and outcomes are quite different. All studies focused on enrolling participants with chronic myofascial pain, but the participants differed widely in the severity of pain and number of trigger points reported and treated. Each study had at least one outcome measure that was a subjective rating scale, including a VAS, an efficacy of treatment verbal scale, and a pain self-rating scale. Additional outcomes could not be compared given the wide variety of measures reported, including SF-36, number of analgesics used per day, pressure pain thresholds, Beck Depression Inventory, number of days/weeks without pain, and Neck Disability Index. Some of these additional outcomes showed promising trends or statistical significance in favor of BoNT treatment, such as taking less analgesic medication per day (Schnider et al. [18]), having fewer days with pain per week (Gobel et al. [15]), and improvements on the SF-36 (Lew et al. [16]).

No study showed an overall statistically significant difference between treatment and control groups. Gobel et al. [15••] reported a short period of statistically significant

Table 2 Summary of randomized controlled trials of intramuscular injections of BoNT for the treatment of thoracic and neck pain

Study	Methods	Participants	Interventions	Outcomes
Cheshire et al. [12]	N: 6 Dropouts: 0 RCT Double blind Crossover	Myofascial pain for 2–4 years	Two injections, one BoNT-A, the other saline, performed 8 weeks apart in random order. 50 U BoNT was distributed at 2–3 sites	4 of 6 participants from the BoNT group “responded” (had improvement of 30 % or greater in VAS scores in at least 2 of the 5 weeks evaluated). 1 of 6 patients did not respond and 1 of 6 patients responded to both BoNT and saline. No statistically significant difference
Esenyel et al. [13]	N: 90 Dropouts: 0 RCT Not blind 5 groups	Unilateral myofascial pain with trigger points in the trapezius for more than 6 months	Groups 1–4 all undertook 15 stretching exercise sessions Group 1: 10 U BoNT-A into a single trigger point, once Group 2: Lidocaine (0.5 %) into one trigger point, once Group 3: Conventional ultrasound to trigger points, 15 sessions Group 4: High power pain threshold ultrasound, 15 sessions Group 5: Control—stretching exercises only	VAS scores evaluated before treatment and at 1 week and 1 month after treatment No statistically significant difference (at 4 weeks, improvement in VAS scores from BoNT was only found to be statistically significant compared with high power pain threshold ultrasound)

Table 2 continued

Study	Methods	Participants	Interventions	Outcomes
Ferrante et al. [14]	N:132 Dropouts: 0 RCT Double blind 2-week washout Dose response 2 groups	Myofascial cervicothoracic pain with 1–5 trigger points for at least 6 months	Single injection trial of 10, 25, or 50 U BoNT-A or saline into each trigger point. All patients received scheduled amitriptyline and ibuprofen and propoxyphene/acetaminophen as needed. All patients received myofascial release physical therapy throughout the study	VAS scores were obtained weekly for 8 weeks following injections. All groups had improved VAS scores compared with the baseline. No statistically significant difference
Gobel et al. [15••]	N: 145 Dropouts: 25 RCT Double blind 2 groups	Moderate to severe upper back myofascial pain syndrome with 10 or more trigger points and pain for 6–24 months	Either 0.9 % NaCl or 40 U BoNT-A was injected into the 10 most painful trigger points at each site	Subjects were followed up every 4 weeks for 12 weeks. Pain was rated on the ordinal pain self-rating scale. Pain diaries were kept from week 1 to week 12. No statistically significant difference (from week 5 to week 8, a statistically significant difference was reached)
Lew et al. [16]	N: 29 Dropouts: 0 RCT Double blind 2 groups	Myofascial upper back pain diagnosed within 2–6 months and current pain score of 5 or greater (VAS) upon enrollment	1–4 muscles were injected with 50 U BoNT or 0.9 % NaCl. No more than 2 muscles per side were injected	Follow up at 0 and 2 weeks and at 1, 2, 3, 4, and 6 months after injection. The 1st two follow-ups were in person. The last five were by mail. (For 26 %, data were not reported.) No statistically significant difference
Ojala et al. [17]	N: 31 Dropouts: 0 RCT Double blind Crossover	Pain in neck and shoulder region for more than 2 months. Clinical diagnosis of myofascial pain	Either saline or 5 U BoNT-A was injected into 3–7 trigger points as the 1st intervention. After 4 weeks, crossover injections were performed	Follow up at 4 weeks after the 1st injection and 4 weeks after the crossover injection. Efficacy of treatment verbal scale reported. No statistically significant difference
Schnider et al. [18]	N: 33 Dropout: 0 RCT Double blind two groups	Diagnosis of cervical headache; 0.5–30 years of symptoms with trigger points	Both groups received standardized physical therapy for 9 sessions. 6 trigger points were treated with 15 U BoNT per site or with 0.9 % NaCl	Headache and muscle tenderness diaries were kept for 16 weeks after injections. The VAS scale was used for headaches and pressure pain threshold was measured for trigger points. Data were reported for successive 4-week periods for 16 weeks. No statistically significant difference

difference in the mean reduction of pain scores between the two groups studied from week 5 to week 8. This study was the highest powered and this result is consistent with the expected time of onset and maximum effect of BoNT, making it a potentially positive result for comparative efficacy of BoNT. From the results of Gobel et al. from a clinical relevance standpoint, the overall improvement in VAS score at 4 weeks was 30 % for the BoNT group and 17 % for the saline group. A13 percentage point difference in mean VAS score between the two groups, although statistically

significant, may not be clinically significant. Fortunately, mean scores do not predict the potential for clinically relevant response to treatment for an individual.

Conclusions

Despite the small number of patients treated in the RCTs of intramuscular injections of BoNT for the treatment of low back pain, two of the three studies discussed showed

statistically significant improvement in VAS scores as compared with placebo injections. Aggregate data cannot be evaluated owing to a large difference in study methodology and heterogeneous patient selections. Additional studies with higher power should be performed to evaluate the validity of existing methodology before new methods are studied given the reported clinical success.

Compared with low back pain, a larger number of patients have been treated in RCTs of intramuscular injection of BoNT for the treatment of myofascial neck and upper back pain. In many cases both BoNT and control treatments produced more than 30 % improvement in subjective pain scores compared with baseline scores. Reports on the comparative efficacy of BoNT and control treatments have only shown trends toward the superiority of BoNT. These results may indicate that the physiologic effects of BoNT on the myofascial pain process are not as important as the simple intervention of needling or injection of NaCl or lidocaine. They could also indicate a poor understanding of which subpopulation of patients with myofascial pain will respond to BoNT. The methods varied widely in BoNT dose, co-interventions, pain severity, chronicity, and number of trigger points treated, so aggregate data evaluation would not be meaningful. Further studies of BoNT treatment for myofascial neck and upper back pain may be able to better characterize the optimal treatment population, dose, and method of administration. It appears that only a small subpopulation of patients with myofascial neck and upper back pain may receive comparative benefit from BoNT treatment given the lack of a statistically significant difference found in multiple studies.

Disclosure J.H. Jung declares no conflict of interest and M.A. Bilezikjian declares no conflict of interest.

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