Botulinum toxin treatment in disabling migraine: a randomized, double-blind, placebo-controlled study

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Introduction

Recent studies demonstrating the effectiveness of botulinum toxin type A (BT-a) in treating several disorders related to muscle spasticity and pain suggest a potential role for this agent in headache treatment.1 The efficacy of BT-a in headache patients was first noted by William Binder, an otolaryngologist, who noted that patients with migraine headaches recovered from their attacks following BT-a injections for the treatment of facial wrinkles.2 Exactly why BT-a is effective in relieving headache is not clear, but mechanisms of actions include direct effects at the neuromuscular junction and direct antinociceptive effects on nerves in the face, head and neck.3

The ability of BT-a to cause muscle paralysis by blocking acetylcholine release at the neuromuscular junction is well known. The toxin produces this effect by proceeding through a sequence of four steps: (a) binding to receptors on the plasma membrane, (b) penetration of plasma membrane by receptor-mediated endocytosis, (c) penetration of the endosome membrane by pH-induced translocation and (d) intracellular expression of an enzymatic action that culminates in blockage of exocytosis.4 BT-a not only reduces acetylcholine release from the alpha motor neuron endings, but also decreases the activity of the muscle spindles by inhibiting the signals from gamma motor neurons and subsequently reducing the Ia afferent signals. In addition, an inhibitory effect on the central pain pathways such as trigeminal ganglion or trigeminal cervical complex in the brainstem have been implicated because suppression of the release of substance P from the dorsal root ganglion5 or calcitonin gene-related peptide (CGRP) from the trigeminal ganglion6 has been shown in animal studies. Focused on an evidence-based method, most of the initial open-labeled reports on BT-a in tension-type headache and migraine were positive. Most recently, these results were, unfortunately, not reproduced as well in controlled trials, suggesting that widespread clinical use of BT-a in headache is not recommended.8

Materials and methods

This was a prospective, randomized, double-blind, placebo-controlled trial of BT-a treatment of migraine headache for 8 months. Injections of BT-a were administered with a 30-gauge needle at sites for a total of 208 units (Dysport ®) to the following targets for each emiscalp: 4 temporalis sites (10 UI each), 4 frontalis sites (6 UI each), 4 upper trapezius sites (10 UI each) for a total of 24 BT-a injections.

Medication dosages for 3 months (if taking such medication), patients with a Migraine Disability Assessment Scale (MIDAS) score of 20 or greater (severe) and Headache Impact Test (HIT-6) score of 60 or greater (very severe impact) at screening, patients able to understand the instructions of the study, complete the questionnaires, and maintain a diary record and willing to give informed consents to be enrolled in the study. Were major exclusion criteria: presence of myasthenia gravis, Eaton- Lambert syndrome, amyotrophic lateral sclerosis or any disease that might interfere with neuromuscular function, concurrent use of amino glycoside antibiotic, curare-like agents, or other agents that might interfere with neuromuscular function, current use of more than one migraine preventative medication or injection of anesthetic or steroid into the muscles to be injected in the month immediately prior to enrollment, the presence of infection at any of the proposed injection sites, patients who were pregnant or breast feeding, previous use of BT-a therapy of any serotype or suspected hypersensitivity to BT-a or any of the ingredients in the formulation, evidence of underlying abnormal pathology contributing to headaches.

The treatment protocol provided a screening for inclusion in the study with medical and medication history, physical and neurological examination, and completion of MIDAS and HIT-6 questionnaires at the screening visit. Patients were provided with headache diaries, for use throughout the study, which included headache type, frequency, intensity, and headache treatment during a 1-month baseline period and for 4 months following BT-a or placebo injections. In addition, patients were given questionnaires related to their satisfaction with headache management. The diary record also included medication use, occurrence of any adverse events, and information regarding performance at work and home using a patient-defined percentage scale of 0% to 100%. Patients meeting inclusion and exclusion criteria were randomized to BT-a or placebo injections.

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Patients maintained a headache diary record during the 4 months following injections and were phoned at 30, 60, and 90 days for an update on their condition. Any headaches occurring during the study period were treated with the patient’s usual migraine therapy; during the period patients were required to complete the MIDAS, HIT-6, and satisfaction questionnaires and diaries every 30 days following injections. At 4 months following the initial injections, patients returned to the hospital for a second round of randomized treatments and were similarly followed every 30 days for 4 months.

The primary outcome measures were the changes in patient’s headache related disability as measured by the HIT-6 and MIDAS disability scales (table 1). Secondary outcome measures included change in headache intensity over the 2 and 4 months periods following injections, patients satisfaction and BT-a treatment safety and tolerability.

Treatment outcomes were analyzed using analysis of variance (ANOVA) and patient satisfaction results were analyzed using Chi-square tests.

Results
The demographic and baseline characteristics of the patients are shown in Table II.

The HIT-6 score declined from baseline values for both BT-a and placebo patients (Figure 1) but the decline was greater for BT-a patients.

The mean changes in HIT-6 scores from baseline were significantly greater for BT-a patients vs placebo at month 1 (6.98 vs 1.08), at month 3 (6.27 vs 1.37), at month 4 (5.53 vs 0.34) and at month 6 (6.19 vs 1.59) (Figure 2).

For patients treated with BT-a, MIDAS scores decreased from a mean score of 74 at baseline to a mean of 38 at month 8 (42% of decrement). For placebo patients, MIDAS scores decreased from a mean of 57 at baseline to 33 at month 8 (42% of decrement).

The percentage of headaches reported as severe in BT-a patients decreased from 32% of all headaches at baseline to 13% by month 8. Severe headaches were therefore experienced 40% less as a proportion of all headaches than at baseline.

Significantly greater percentages of BT-a patients expressed satisfaction with their headache for 6 of the 8 months as compared with placebo patients and there appeared to be a progressive benefit following a repeat BT-a treatment at month 4. Moreover, we don’t appreciate any adverse event.

Discussion
Focused on an evidence-based method, most of the initial open-labeled reports on BT-a in tension-type headache and in migraine were positive. Most recently, these results were, unfortunately, not reproduced as well in controlled trials. Selection of appropriate candidates for preventive therapy begins with accurate headache diagnosis and classification. According to these rules, BT-a therapy may be appropriate for: patients with disabling primary headaches, patients who have failed to respond adequately to conventional treatments, patients with unac-
ceptable side effects (from existing treatments), patients in whom standard preventive treatments are contraindicated, patients in special populations or situations, patients missing, abusing or overusing medications, patients with coexisting jaw, head or neck muscle spasm and patients who prefer this treatment. There is no established or standardized methodology for the injection of BT-a for migraine and tension-type headache. BT-a is administered either at fixed injection sites, at sites of pain or tenderness ("follow the pain") or a combination of both. The clinical dose of BT-a commonly used for migraine therapy is between 25–200 units (Botox) and 100–500 units (Dysport); the number of injected sites may vary from 10 to 25. However, the total dosage of toxin administered, the number of units per site of injection, dilution of toxin and sites of injection varied widely between studies. Current data do not appear to indicate a dose response benefit. Therefore, there is a need for further studies in order to identify the minimal effective dosage and optimal individualized dosing regimen. On the other hand, some data report a greater efficacy with repeated dosing. This may be because repeat injections have a step-like therapeutic effect: the consecutive therapeutic effect of each injection builds on the effect previously achieved.

Conclusions
The efficacy and safety profile of BT-a suggest that it is an effective, well tolerated prophylactic treatment in migraine patients with chronic daily headache who are not using other prophylactic headache treatments. BT-a treatment significantly reduced the impact associated with migraine compared with placebo and was associated with improvements in the disability associated with migraine. We observed that the treatment led to a greater patient satisfaction, and the long-term, continued benefit speaks against placebo effect. Besides the injections were safe and well tolerated. Taken together, the data also suggest that assessment of the frequency of headache is a sensitive measure of efficacy in this patient population, but future studies to confirm these findings are needed. The optimal dosing and injection regimens are not yet known. The dosage ranges usually administered are effective and adverse side effects, which are often mild to moderate, are transient; however they appear to be dose-dependent. A combination of fixed anterior injections with a follow-the-pain approach appears to be optimal, but further studies are necessary to determine the most effective injection regimens. Another aspect is the frequency of treatment, which seems to have a cumulative effect with subsequent injections. The data at this time do not support the efficacy of BT-a for the treatment of episodic migraine or tension type headache but in large studies, the subgroup analysis suggest that headache frequency may be reduced in patients free from other preventive medications. Further evidence is needed to determine whether BT-a can serve as a first-line therapy for patients with less refractory headaches, and to determine optimal injection sites, doses and frequency of treatment.

Abstract
Botulinum toxin type A (BT-a) has been shown to effectively treat severe types of neurological disorders. For over 15 years it has been used clinically also for the prophylaxis and treatment of various types of primary headache disorders. Although BT-a efficacy has not been proven in tension-type headache, its use in migraine continues to cause controversy. There is adequate data to support the hypothesis, beside its well known effect on acetylcholine release, of an additional antinociceptive action related to a block in the local release of nociceptive neuropeptides. We tried to evaluate the efficacy of botulinum toxin type A treatment in reducing the disability associated with migraine. Patients were randomized to receive BT-a or placebo, administered after a 1-month baseline period and repeated after 4 months; they were assessed every 30 days.

References