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From Headache

Botulinum Toxin A in the Treatment of Chronic Tension-Type Headache With Cervical Myofascial Trigger Points: A Randomized, Double-Blind, Placebo-Controlled Pilot Study

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Authors and Disclosures

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Abstract and Introduction

Abstract

Objective: To evaluate the efficacy of botulinum toxin A (BT-A) as a prophylactic treatment for chronic tension-type headache (CTTH) with myofascial trigger points (MTPs) producing referred head pain.
Background: Although BT-A has received mixed support for the treatment of TTH, deliberate injection directly into the cervical MTPs very often found in this population has not been formally evaluated.
Methods: Patients with CTTH and specific MTPs producing referred head pain were assigned randomly to receive intramuscular injections of BT-A or isotonic saline (placebo) in a double-blind design. Daily headache diaries, pill counts, trigger point pressure algometry, range of motion assessment, and responses to standardized pain and psychological questionnaires were used as outcome measures; patients returned for follow-up assessment at 2 weeks, 1 month, 2 months, and 3 months post injection. After 3 months, all patients were offered participation in an open-label extension of the study. Effect sizes were calculated to index treatment effects among the intent-to-treat population; individual time series models were computed for average pain intensity.
Results: The 23 participants reported experiencing headache on a near-daily basis (average of 27 days/month). Compared with placebo, patients in the BT-A group reported greater reductions in headache frequency during the first part of the study ($P = .013$), but these effects dissipated by week 12. Reductions in headache intensity over time did not differ significantly between groups ($P = .80$; maximum $d = 0.13$), although a larger proportion of BT-A patients showed evidence of statistically significant improvements in headache intensity in the time series analyses (62.5% for BT-A vs 30% for placebo). There were no differences between the groups on any of the secondary outcome measures.
Conclusions: The evidence for BT-A in headache is mixed, and even more so in CTTH. However, the putative technique of injecting BT-A directly into the ubiquitous MTPs in CTTH is partially supported in this pilot study. Definitive trials with larger samples are needed to test this hypothesis further.

Introduction

Tension-type headache (TTH) is the most prevalent of all the primary headache disorders[1] and is associated with significant costs to both headache sufferers and society as a whole.[1-3] Despite awareness of the prevalence and impact of TTH, much work remains in establishing pathophysiological mechanisms and identifying effective treatments. Travel originally outlined characteristic patterns of head pain referred from cervical myofascial trigger points (MTPs).[4] Subsequent work has confirmed a role for myofascial and musculoskeletal abnormalities of the neck and shoulders that contribute to headache-related symptomatology.[5]

Although the histopathology of these MTPs is largely unknown, there is mounting evidence that there are pathophysiologic abnormalities in TPs in both humans and animals.[6,7] Specifically, electrodiagnostic studies have confirmed that MTPs are associated with motor endplate abnormalities and increased release of acetylcholine, becoming areas of focal spasm and ischemia secondary to sustained sarcomere contraction; the long-term result of this process is nociceptive sensitization, chronic pain, and a repeated positive feedback cycle among these interacting variables that perpetuates pain.[6] Most recently, referred pain from cervical MTPs has been implicated in the relationship between central sensitization and chronic pain characteristic of chronic TTH (CTTH).[8-10] Studies have shown that CTTH patients report a larger number of MTPs than do nonheadache controls[5] and that active and bilateral MTPs are associated with greater headache intensity and frequency in CTTH patients than are latent and unilateral MTPs.[10-12] According to current thinking, CTTH is thus at least partly a function of referred pain from

these multiple TPs in the head, cervical, and shoulder muscles; these hyperalgesic zones ultimately contribute to central sensitization mediated by dorsal-horn neurons.[10]

Historical management of MTPs has entailed conservative strategies including stretching exercises, massage, ice, and myofascial release, as well as more aggressive interventions such as dry needling, local anesthetic injections, isotonic saline injections, and pharmacotherapy.[6] Most recently, botulinum toxin A (BT-A; Botox®, Allergan Inc., Irvine, CA, USA) has been investigated as an alternative treatment modality. BT-A is a potent naturally occurring toxin which, when administered intramuscularly in very small doses, causes dose-dependent muscular relaxation by inhibiting the release of acetylcholine at the neuromuscular junction.[13] Although negative studies exist,[14] there is some recent evidence that BT-A may have beneficial effects for patients suffering from various neck- and shoulder-related disorders associated with headache, such as cervical dystonia[15] and myofascial pain syndrome.[16-18]

Contemporary literature on the treatment of TTH also shows mixed support for BT-A. While several case reports and uncontrolled or open-label studies have reported positive findings,[19-22] results from controlled studies have been mixed. Some investigators have obtained positive results with small[23] or mixed headache samples,[24] while others have reported positive findings on secondary outcome measures only.[25-27] Many other studies specifically focused on TTH and CTTH have reported negative results when comparing BT-A to placebo or viable comparison treatments,[28-30] even when EMG evidence confirms reduced muscle activity following BT-A treatment.[31] Regarding CTTH specifically, a 2008 report of the American Academy of Neurology concluded that BT-A was "probably ineffective" for CTTH,[32] although this report did not focus on CTTH as related to MTPs. Notably, a recent study found that 4/11 patients responded favorably to BT-A, and the presence of pericranial muscle tenderness was predictive of a positive response to treatment.[33] To our knowledge, no published studies have evaluated BT-A as a treatment for CTTH in patients with specific cervical MTPs that, when palpated, produce referred head pain corresponding to the patient's headache pattern (as per Travel and Simons[4]).

The present study endeavored to evaluate the efficacy of BT-A for CTTH patients with cervical MTPs. Patients were randomly assigned to receive double-blinded BT-A or saline injections directly into identified trigger points. Measures of headache frequency, headache intensity, and range of motion (ROM) were assessed at baseline and for 12 weeks post injection. Additional measures of pain-related disability, headache self-efficacy, depression, and anxiety also were assessed over time.

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Botulinum Toxin A in the Treatment of Chronic Tension-Type Headache: Methods

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Methods

The study used a randomized, double-blind, placebo-controlled design. All participants provided informed consent. The study was approved by Northwestern University's Institutional Review Board and conducted according to the Declaration of the Helsinki conventions.

Patients

Participants were recruited from the outpatient clinic of the Center for Pain Studies at the Rehabilitation Institute of Chicago, as well as by newspaper advertisements. Patients were selected for inclusion if they were at least 18 years of age, met IHS criteria[34] for CTTH, had identifiable cervical MTPs that referred pain corresponding to the their characteristic headache pattern, and had no other significant pain problems. Exclusion criteria included pregnancy or breastfeeding, daily opioid prophylaxis, prior BT-A therapy, significant depression or anxiety, present involvement in physical or occupational therapy, history of treatment noncompliance, or conditions or medication regimens that might interfere with neuromuscular transmission (eg, myasthenia gravis, amyotrophic lateral sclerosis, muscular atrophy or infection at injection sites, use of aminoglycoside antibiotics).

Measures

Pressure Algometry Trigger Point Assessment. At baseline evaluation and at each follow-up visit, patients underwent a standardized assessment of MTP pressure sensitivity using a pressure algometer (Fischer algometer [35,36]).

Each algometry assessment examined cervical/trapezial muscles including the upper border of the trapezius, the belly of the sternocleidomastoid (sternal or clavicular division), and the belly of the splenius capitis (which overlies other involved cervical muscle groups such as the semispinalis capitis, longissimus capitis, recti capitis posterior, and obliqui capitis superior), all of which are common trigger point locations.[4] Outcomes consisted of raw scores at each of 4 most active points (eg, those with the lowest threshold that recreated the headache pain), as well as an overall trigger point algometry summary score of the sum of the thresholds of these points for each evaluation time point.

Cervical ROM Assessment. Forward flexion, neutral extension, lateral rotation - right, lateral rotation - left, side-bending - right, and side-bending - left were assessed using a goniometer (rotation) and an inclinometer (bending).

McGill Pain Questionnaire-short Form (MPQ-SF). [37] The MPQ-SF is a well-validated pain measure which permits separation of the sensory, affective, and evaluative components of pain. This measure also contains a 101 mm visual analog scale (VAS) for assessing pain intensity. The MPQ-SF was administered during clinic visits at baseline, after injection, and at each follow-up.

Beck Depression Inventory (BDI). [38] The BDI is a well-validated, 21-item self-report measure on which respondents rate the severity of various depression symptoms experienced over the preceding 2 weeks.

Headache Specific Self-efficacy Scale (HSES). [39] The HSES is a 51-item questionnaire designed to assess recurrent headache sufferers' belief in their ability to control their headaches.

State Trait Anxiety Inventory (STAI). [40] The STAI is a widely used, 40-item self-report measure of cognitive, affective, and physiological manifestations of anxiety. Twenty items inquire about current symptoms (State subscale) and 20 inquire about more longstanding symptoms (Trait subscale). For the present study, only the Trait subscale was used.

Pain Disability Index (PDI). [41] The PDI is a 7-item, validated instrument that assesses patient-perceived disability in 7 life areas, providing a total score of pain-related disability.

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Daily Diaries. Patients completed a daily diary to indicate the pain intensity of their headaches (at breakfast, lunch, and dinner times). Pain intensity was self-reported using both the VAS (0-100) and evaluative components from the MPQ-SF. Mood was self-reported once per day (at dinner time) using the Profile of Mood States-Short Form.[42]

Pill Counts. On each visit, the amount of rescue medication (Etodolac) used was counted to serve as a secondary outcome measure. Greater rescue medication usage was considered an indicator of less adequate overall pain control.

Procedure

On the initial visit, patients provided informed consent then completed a medical history, physical examination, pressure algometer evaluation, and ROM assessment. They also completed the pain-related and affective questionnaires described earlier and were provided 42 tablets of a "gastrointestinal-protective" nonsteroidal anti-inflammatory drug, Etodolac, for use as a rescue agent throughout the study to be used no more often than twice a day. Prescriptions for Etodolac were refilled as needed at each subsequent visit. Patients were asked to refrain from using any other pain or anti-inflammatory medications for the duration of the study and were precluded from using rescue medication within 8 hours prior to their appointment on any day of testing. Patients then underwent a baseline phase during which they completed the daily diary as well as a record of their use of the rescue medication for 2 weeks.

After the baseline period, patients returned and again completed the MPQ and PDI. Their daily diaries were reviewed and pill counts were obtained. They then received randomized, double-blinded BT-A or isotonic saline injections into the 4 most sensitive trigger points identified in the physical exam (as above). The BT-A was reconstituted and diluted in 1 mL of saline. Dosage was 25 units per trigger point with no more than 100 units total per patient (ie, no more than 4 trigger points treated per patient). The same volume of isotonic saline (1 mL) was injected in the same manner in the control patients. Two physicians (JC and PJ) experienced in the intramuscular administration of BT-A performed all injections. After the injections, patients again completed the MPQ and underwent pressure algometer and ROM assessment.

Follow-up appointments were scheduled for 2 weeks, 1 month, 2 months, and 3 months post injection. In the interim, patients continued to keep a daily diary of their headache activity. At each follow-up, daily diaries were retrieved and pill counts recorded; patients also completed the MPQ and PDI and underwent the pressure algometer and ROM assessments. At the 3-month follow-up patients completed the pain-related and affective measures from the initial session and were asked to assess the global efficacy of treatment. Patients were then provided the opportunity to participate in an open-label extension of the study, during which all patients (both groups) received BT-A injections in identified trigger points. Patients completed daily diaries for a period of 3 additional months, and returned for monthly follow-up assessments during this period. Follow-up assessments were the same in content to those of the controlled trial.

Statistical Analyses

This study was conducted as a pilot effort to estimate effect sizes that would inform a larger trial. Thus, for all primary analyses, a standardized measure of effect size, Cohen's *d*, is reported to index the size of the observed differences between treatment groups.[43] The *d* statistic is reported in standard deviation units and can range from 0 (no group differences) to any positive number (larger numbers indicate larger differences). Although the interpretation of *d* varies based on the clinical significance of what is being measured, $d = 0.20$ has been called a "small" difference, $d = 0.50$ a "medium" difference, and $d \geq 0.80$ a "large" difference. [43] Although formal significance testing was conducted, primary emphasis is placed on evaluation of the size of the observed effects because of the relatively small group sample sizes.

Analyses were conducted on the intent-to-treat population, which was defined as all randomized patients who provided at least 1 post randomization efficacy evaluation (ie, completed a postbaseline diary entry). Analyses were conducted using SPSS 15.0 (SPSS, Inc., Chicago, IL, USA). Significance of 2-tailed tests was interpreted at $P < .05$.

For the primary outcome measures of headache intensity and headache frequency, patients' daily diary entries were averaged to create treatment periods corresponding to 2-week intervals. Missing values were imputed using the last observation carried forward approach. Generalized estimating equations were then applied to account for the repeated measurements within individuals. For both headache intensity and frequency, a 2 x 7 model was specified with Group (BT-A vs Placebo) as a between-subjects factor and time (baseline, weeks 1-2, weeks 3-4, weeks 5-6, weeks 7-8, weeks 9-10, weeks 11-12) as a repeated measures factor. No formal significance tests were conducted on the open label portion of the study because of the fact that participation in this phase of the study was optional and consented to separately from the double-blind phase (ie, participant group status was self-selected).

For the secondary outcomes of ROM, trigger point threshold, and the psychological measures that were assessed at 2 time periods (pretreatment and at week 12), an ANCOVA was conducted with group (BT-A vs placebo) as a between-subjects factor and pretreatment value as a covariate. In light of recent interest in using responder analyses for BT-A treatment studies,[33] individual patient analyses also were conducted with the application of individual time series models created for each patient's headache intensity (average of VAS scores for a given day). For these analyses, Autoregressive Integrated Moving Average (1,0,0) models were used to examine average pain reports in relation to a patient's baseline. To control for multiple comparisons within each subject, the significance value for these analyses was set to a conservative $P < .009$ per patient.

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