

Botulinum Toxin Type A as an Effective Prophylactic Treatment in Primary Headache Disorders

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Objective.—To measure the effect of botulinum toxin type A (Botox, Allergan, Inc, Irvine, CA) treatment in 271 patients diagnosed with headache in accordance with International Headache Society (IHS) criteria.

Background.—Botulinum toxin type A has shown promise for the treatment of headache in several clinical trials, but uncertainty remains as to how botulinum toxin type A optimally should be used for treating headache and which patients are best suited for this treatment.

Methods.—This was a retrospective chart review of all patients who received botulinum toxin type A for the treatment of headache from January 1999 to February 2002. Patients were injected with an average dose of 63.2 U (SD, 14.5) of botulinum toxin type A on 2 or more visits, with treatments involving a “fixed-site” or a “follow-the-pain” (or a combination of both) approach. In the fixed-site approach, botulinum toxin type A was injected into the procerus, corrugator, frontalis, and temporalis muscles. In the follow-the-pain approach, botulinum toxin type A was injected into a combination of the procerus, corrugator, frontalis, temporalis, occipitalis, trapezius, and/or semispinalis capitis muscles. The primary outcomes for the trial were the reduction in headache days per month or headache intensity (0 to 3 scale) (or both) from baseline. Patients were diagnosed according to IHS criteria and subsequently classified into the following categories: chronic daily headache (more than 15 headache days per month), episodic tension-type headache, episodic migraine, and “mixed” HA (less than 15 headache days per month, combination of migraine and tension-type headache).

Results.—Treatment period was an average of 8.6 months (SD, 6.4); patients received an average of 3.4 doses (SD, 1.6) 3 months apart. Of the 271 patients, 29 (10.7%) had episodic migraine, 17 (6.3%) had episodic tension-type headache, 71 (26.2%) had mixed headache, and 154 (56.8%) had chronic daily headache. Two-hundred fifty-six patients had data for the number of headache days per month, 117 had data for headache intensity, and all 271 had data for headache days or headache intensity. Botulinum toxin type A treatment significantly reduced the number of headache days per month from 18.9 (SD, 10.3) to 8.3 (SD, 8.9) ($n = 256, P < .001$)—a 56% reduction. Headache intensity decreased from 2.4 points (SD, 0.6) to 1.8 points (SD, 0.8) ($n = 117, P < .001$)—a 25% reduction. Of 263 patients surveyed, 225 (85.6%) reported improvement in headache frequency and intensity. There was no correlation of effect/lack of effect with reason for treatment, duration/number of treatments, injection technique, mean/total dose, age, gender, or comorbidity. Approximately 95% of patients did not experience medication side effects.

Conclusion.—These results suggest that botulinum toxin type A may be an effective and safe prophylactic treatment for a variety of moderate to severe chronic headache types.

Key words: migraine, prophylactic, botulinum toxin type A

Abbreviations: HA headache, CDH chronic daily headache, BoNT-A botulinum toxin type A

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Headache (HA) is one of the most common neurologic symptoms in clinical practice and is broadly classified into chronic and episodic types. Headache

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presenting for more than 15 days per month and lasting more than 4 hours per day is classified as chronic daily HA (CDH).¹ About 5% of the general population, including 9% of women, is affected by CDH. For a significant number of patients, CDH is thought to originate as migraine in which the frequency of attacks increases until a pattern of daily HA evolves.¹

Migraine is a common neurologic disorder that can be episodic or chronic. Data from the American Migraine Study II estimated that approximately 18% of women and 6% of men experience migraine, with the disorder affecting approximately 28 million Americans in 1999.² The prevalence and distribution of migraine, according to this survey, have remained stable over a 10-year period,² with an overall increase in the rate of diagnosis (from 38% to 48%) over the same period.³

The stated goals of long-term HA treatment are to reduce the frequency, severity, and disability associated with migraine attacks; decrease the reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies; and avoid acute HA medication escalation.⁴ To accomplish these goals, preventive or prophylactic treatment may be necessary. Preventive therapy may improve functional ability and responsiveness to treatment of acute attacks.^{4,5}

Pain relief associated with the use of botulinum toxin type A (Botox, Allergan, Inc, Irvine, CA) (BoNT-A) for the treatment of cervical dystonia and spasticity has been frequently reported.⁶⁻⁹ Botulinum toxin type A is a novel prophylactic HA treatment that, through its actions on the neuromuscular junction, has muscular effects without vascular or systemic effects. Botulinum toxin type A has shown promise for the treatment of HA in several clinical trials,^{4,10} but uncertainty remains as to how BoNT-A optimally should be used for treating HA and which patients are best suited for this treatment.

The hypothesis was that BoNT-A injected into the head and neck regions would prevent HA in patients with migraine, tension-type HA (TTH), CDH, or mixed HA. A retrospective chart review was therefore undertaken to document the response of HA to BoNT-A treatments used as preventive therapy for HA disorders encountered in the clinic from January 1999 to February 2002.

METHODOLOGY

This was a retrospective chart review of the period from January 1999 to February 2002. A data extraction sheet was used for each patient to evaluate the effect of BoNT-A as a prophylactic treatment for pri-

mary HA disorders. All patients diagnosed with HA according to International Headache Society (IHS) criteria and injected with BoNT-A were included in the study and subsequently classified according to HA features, including CDH (more than 15 HA days per month), episodic tension-type HA (ETTH), episodic migraine, and mixed HA (less than 15 HA days per month, combination of migraine and TTH). Verbal or written consent was obtained after a review of the known adverse events of treatment including possible HA, rash, bruising, or eyebrow and eyelid ptosis. Patients were further informed that injection-site blebs (fluid collection) that normally occur in the forehead region usually disappear within a few hours. Instructions regarding the use of oral medications, other HA treatments, and a HA diary were provided. The patient was informed that the time of onset of treatment effects is between 3 to 14 days, and the duration of action is approximately 12 to 16 weeks. The patient was questioned regarding the anatomic location of the HA, and the frontalis, temporalis, and posterolateral neck and shoulder regions were palpated to identify areas of tenderness.

Dilutions of 1 vial (100-U BoNT-A) were accomplished with 2 or 4 mL of preservative-free 0.9% saline (5.0 or 2.5 U/0.1 mL, respectively). The total dose of BoNT-A to be administered was determined by adjusting for the specific features of the patient (type of HA, severity of symptoms, body size, head or neck region). The injection approach chosen and the doses used were in accordance with the author's clinical experience, as no formal guidelines for the use of BoNT-A treatment of HA currently exist.

After placing the patient in a sitting or supine position, intramuscular injections using proper sterile techniques were administered using 1-mL, 30-gauge, one-half-inch tuberculin syringes. (Intra-arterial injections of BoNT-A should be avoided.) Botulinum toxin type A treatment was administered using a fixed-site or follow-the-pain (or a combination of both) approach dependent upon the patient's complaint and the physician's examination. The fixed-site approach was employed in any patient with migraine features, while the follow-the-pain approach was used for any patient with TTH. Both approaches were used in

patients with features of mixed HA. For the fixed-site approach, BoNT-A was injected into the procerus (5 U, 1 site), corrugator (2.5 U each, 2 sites [medial and lateral]), frontalis (2.5 U each, 5 sites on each side), and temporalis (2.5 U each, 4 sites on each side) muscles (Figure 1). For the follow-the-pain approach, BoNT-A was injected into the frontalis (2.5 U each, 5 sites on each side), temporalis (2.5 U each, 4 sites on each side), occipitalis (2.5 to 5 U on each side), trapezius (7.5 to 15 U on each side), semispinalis capitis (7.5 to 15 U on

each side), and/or splenius capitis muscles, as deemed appropriate (Figure 1).

The primary efficacy outcome measures were reduction in HA frequency and intensity, and the data were collected and recorded at baseline, at each clinic visit, and at last treatment. Patients reported HA frequency and intensity in HA diaries as an average since the last treatment visit, usually a 3-month period. After baseline, HA data were collected, and the patients were then injected; therefore, the baseline visit

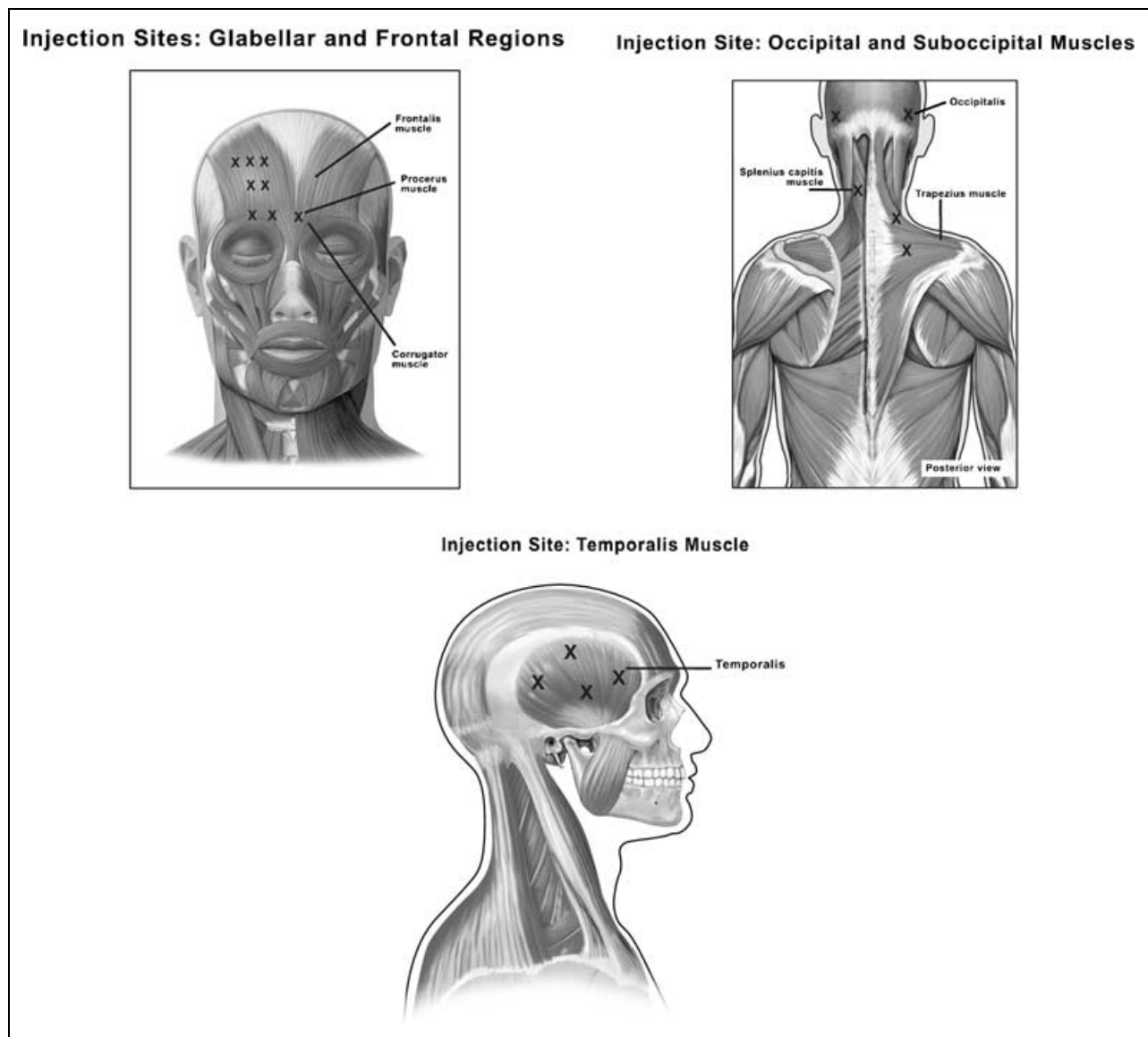


Fig 1.—Injection sites for botulinum toxin type A treatment. Copyright (c) 2003. Nucleus Medical Art, All Rights Reserved. www.nucleusinc.com

was also the first treatment visit. Patients received the next BTXA dose after the previous dose had completely worn off and HA returned.

The data excluded from the analysis included patients with only one BoNT-A treatment, time between visits greater than 1 year, and missing data. There had to be HA frequency data or HA intensity data for both the baseline and last treatment visits. The number of headache days per month measured headache frequency for 256 patients, and HA intensity was recorded for 117 patients using a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). At the last treatment, patients were asked to assess their symptoms compared with those at baseline. Only the data from the patients' baseline visit and last treatment visit were analyzed based on a verbal report from their HA diaries. All data included in this study is, therefore, based on approximately a 3-month period.

Analyses of efficacy parameters were performed using paired-sample statistics, analysis of variance (ANOVA), and chi-square tests. Preinjection and postinjection scores for HA days, HA intensity, and patients' subjective reports were evaluated for any correlative effects due to age, gender, comorbid condition(s), reason(s) for seeking treatment, months of treatment, number of treatments, average and total BoNT-A dose, and injection technique using either a paired *t* test or a chi-square analysis.

This study was conducted in compliance with institutional review board regulations, informed consent regulations, the Declaration of Helsinki, and the IHS guidelines for studies of the prevention of migraine.

RESULTS

Patient Population.—The mean age of the 271 patients in this study was 48.6 years (SD, 11.7); 222 patients (81.9%) were women (Table). Chronic daily headache accounted for 154 patients (56.8%), while migrainous features (episodic migraine and mixed HA) were present in 100 patients (36.9%) who had less than 15 HA days per month. The remaining 17 patients (6.3%) had ETTH. The main reasons for patients seeking BoNT-A treatment were refractory response to oral medications ($n = 209$; 77%) and acute

Patient Characteristics*

Feature	Patient Population (N = 271)
Age, mean (SD), y	48.6 (11.7)
Gender	
Female	222 (81.9)
Male	49 (18.1)
Headache type	
Episodic migraine	29 (10.7)
Chronic daily	154 (56.8)
Episodic tension	17 (6.3)
Mixed	71 (26.2)
Comorbidities [†]	
Depression	92 (33.9)
Hypertension	26 (9.6)
Chronic pain syndrome	26 (9.6)
Seizures	1 (0.4)
None of the above	147 (54.2)
Reasons for seeking treatment [†]	
Refractory to oral medications	209 (77.1)
Medication overuse	131 (48.3)
Tender neck/shoulder	49 (18.1)

*Values are number (percentage) unless otherwise indicated.

[†]Total number exceeds 271 because patients could present with more than one comorbid condition and more than one reason for seeking treatment.

medication overuse ($n = 131$; 48%). Depression was a frequent comorbidity in this patient population, occurring in 92 patients (34%), whereas hypertension occurred in 26 patients (9.6%).

Botulinum Toxin Type A Treatment.—The mean BoNT-A dose was 63.2 U (SD, 14.5; range, 21 to 162.5). The mean total treatment period was 8.6 months (SD, 6.4) during which time patients received an average of 3.4 treatments (SD, 1.6) of BoNT-A (all were treated at least twice), approximately 3 months apart. Of the 271 patients, 256 had data for the number of HA days per month, 117 had data for HA intensity, and all 271 had data for HA days or HA intensity.

Botulinum toxin type A treatment significantly reduced HA frequency. The number of HA days per month decreased from 18.9 (SD, 10.3) at baseline to 8.3 (SD, 8.9) at last treatment ($n = 256$, $P < .001$)—a 56% reduction (Figure 2). Significant reductions in HA frequency were observed regardless of HA type (all, $P < .001$). Headache intensity decreased

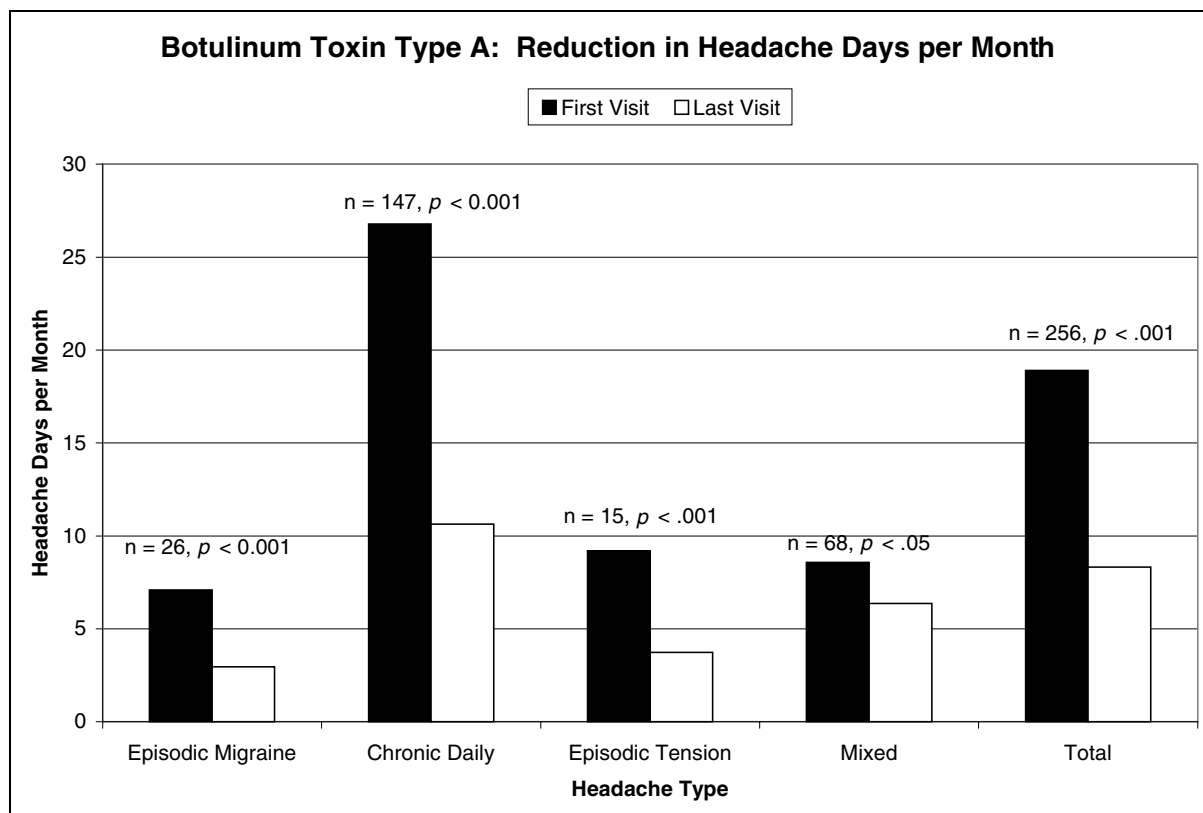


Fig 2.—Reduction in headache (HA) days per month with botulinum toxin type A treatment. Headache days decreased 56%, and HA frequency significantly declined, regardless of HA type (all, $P < .001$).

significantly from 2.4 points (SD, 0.6) at baseline to 1.8 points (SD, 0.8) at last treatment ($n = 117, P < .001$)—a 25% reduction (Figure 3). Headache intensity scores were significantly lower for patients with episodic migraine ($n = 15, P < .001$), CDH ($n = 67, P < .001$), and mixed HA ($n = 29, P < .05$), but were not significant for ETTH ($n = 6, P = .09$).

Overall, 85.6% of patients surveyed (225 of 263) reported improvement in their symptoms with BoNT-A treatment. Age, gender, comorbid condition(s), reason(s) for seeking treatment, months of treatment, number of treatments, average or total BoNT-A dose, or injection technique did not predict the response on any of the outcome measures studied, as no statistical relationship was found.

Safety.—Ptosis of the eyelid was reported in 3 patients (1.1%) and ptosis of the eyebrow in 3 (1.1%). Neck muscle weakness was reported in 3 patients (1.1%) and 5 patients (1.8%) reported “other” adverse events, defined as flu-like symptoms or HA. No adverse events were reported in 257 patients

(94.8%). Adverse events were mild and transient in nature.

COMMENTS

In this study, BoNT-A was shown to be an effective, safe, and well-tolerated prophylactic treatment for patients with a range of moderate to severe chronic HA types, the majority (77%) of who were refractory to oral medications. In addition, a little over one third of patients (33.9%) had comorbid depression and 9.6% of patients had hypertension, with an equal percentage having chronic pain syndrome. Patients with such chronic conditions tend to require a variety of prescription drugs, but the absence of any meaningful drug interactions associated with BoNT-A treatment may lessen the potential concern often associated with multiple treatment regimens. Approximately 95% of patients reported no adverse events. Botulinum toxin type A use significantly reduced HA frequency and intensity in these patients. No specific factors, such as prior treatment, comorbid depression, age,

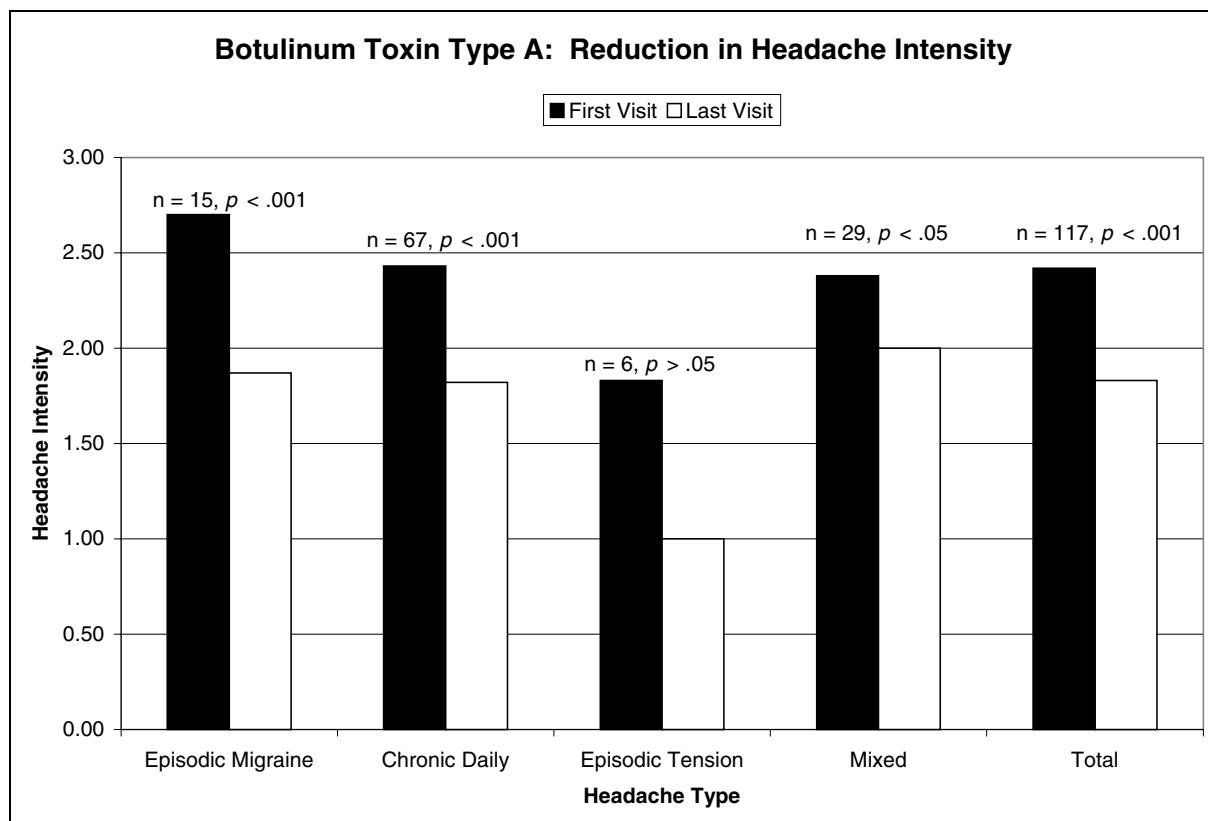


Fig 3.—Reduction in headache (HA) intensity with botulinum toxin type A treatment. Headache intensity decreased 25%; HA intensity significantly decreased for patients with chronic daily headache, episodic migraine, and mixed HA, with a trend toward significance for episodic tension-type HA.

gender, or HA type or intensity, prevented response to treatment.

Patients were treated in this study using a fixed-site approach, a follow-the-pain approach, or a combination of the 2, according to patient need. The injection technique employed can be critical to treatment success and minimizing the risk of adverse events. Avoiding the inferolateral frontalis regions (lateral suprabrow areas) may reduce the risk of lid or brow ptosis, and avoiding the superficial veins may minimize the risk of bruising. The injection sites commonly utilized for BoNT-A injection for the treatment of HA are the glabellar and frontal regions, temporalis muscle, suboccipital region, and splenius capitis.^{10,11-13} The high degree of efficacy seen in this study in comparison with previous studies may be related to the dose, injection sites, and injection methodology used.

Smuts et al conducted a 4-month, randomized, double-blind, placebo-controlled trial in 37 patients with chronic tension-type HA (CTTH).¹⁰ Botulinum

toxin type A (100 U in 2 mL saline), divided into two 1-mL doses equivalent to 50 U of the drug, was administered to each side of the patient's head. Using electromyographic guidance, 2 sites in the temporal muscles and 4 sites in the cervical muscles were then injected. Compared with pretreatment rates, statistically significant improvements in HA intensity ($P = .002$) and HA-free days ($P = .001$) were evident by month 3.

In contrast, Schmitt et al conducted a 2-month, randomized, placebo-controlled study to examine the effect of 20 U BoNT-A injected into frontal and temporal muscles in 60 patients with CTTH.¹⁴ Important outcome variables such as pain intensity, number of pain-free days, and consumption of analgesics were not statistically different between the groups after 2 months. The relatively low dose (20 U) may have reduced the impact of treatment. Furthermore, the lack of a cervical muscle injection site and the short duration of follow-up may also have

prevented separation between BoNT-A and placebo groups.

It is hypothesized that the difference in results of these 2 trials reflects the importance in the selection of dose, number and location of injection sites, length of treatment, and type of patient—all of which are thought to be critical factors in determining the success of BoNT-A treatment in HA.

Studies have also shown that BoNT-A has promise in treating migraine. Binder et al conducted an open-label, multicenter trial of BoNT-A treatment of 106 predominantly female patients with migraine.¹¹ Among 77 true migraineurs treated prophylactically, 89% reported complete or partial response.

Silberstein et al conducted a prospective, double-blind, vehicle-controlled study of BoNT-A treatment in 123 patients with a history of 2 to 8 moderate to severe migraine attacks per month, with or without aura.¹² Patients were randomized to receive single administrations of vehicle or BoNT-A, 25 or 75 U, injected into multiple sites of pericranial muscles at the same visit. During a 1-month baseline period and for 3 months following injection, patients kept daily diaries in which they recorded migraine frequency, migraine severity, and the occurrence of migraine-associated symptoms. Compared with those receiving vehicle, patients receiving 25-U BoNT-A, but not 75 U, showed a significantly greater reduction in moderate to severe migraine frequency at month 2 ($P = .008$) and at month 3 ($P = .04$). There was a significantly greater reduction in mean severity at months 1 and 2 ($P < .029$). These patients also experienced a reduction in the number of migraines of any severity at month 3 ($P = .01$). Patients on 25 U also experienced a reduced number of days using acute migraine medications at month 2 ($P = .03$) and a reduced incidence of migraine-associated vomiting at month 3 ($P = .01$). It is not clear why the 75-U dose did not perform as well as the 25-U dose in this study. The authors speculated that it was perhaps due to the lower frequency of migraines at baseline in that treatment group.¹²

The results from these studies add to the evidence of the efficacy of BoNT-A in treating migraine HA and potentially TTH, even though the precise mechanism by which the head pain is reduced is unclear. Based on limited in vitro and in vivo data, it is possible

that BoNT-A treatment may reduce the local release of nociceptive neuropeptides.^{15,16} In the fixed-site approach employed in this study for HA with migraine features, the injection sites chosen were in close proximity to the trigeminal nerve, which is believed to be important in the pathogenesis of migraine.¹⁷ Guyuron et al postulate that perhaps the nerves are stimulated by strong contraction of the corrugator supercilii and the temporalis muscles.^{18,19} It is possible that BoNT-A, by relaxing the corrugators, inhibits the triggering of a migraine attack.

Clinical and preclinical studies performed to date suggest that BoNT-A may work at multiple points in the pathophysiologic cascade of HA, although it is not yet clear which of these points are quantitatively the most important. There are likely multiple components to the pathophysiology of HA. Further work in this area is necessary to provide additional insight into the role of BoNT-A as a prophylactic treatment in different HA types.

The results reported here add to the increasing evidence of the efficacy and safety of BoNT-A treatment in a variety of HA types including migraine. Further studies are needed to clarify the best dosing, choice and number of injection sites, and injection technique required to provide optimal treatment outcomes and to define those patients who respond most favorably to this treatment.

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