Botulinum Toxin A (BOTOX®) for Chronic Daily Headache: A Randomized, Placebo-Controlled, Parallel Design Study

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ABSTRACT

Introduction: Satisfactory treatments for chronic daily headache (CDH) are lacking. Botulinum toxin A (BTX) has been reported to help both migraine and tension headaches. **Methods:** Sixty patients with headaches of more than 15 days per months were recruited for this double-blind, placebo-controlled, parallel study. The primary efficacy point was a headache diary. Secondary efficacy points included global impressions, the use of abortive headache medications, palpation scores (rated 0-4 at 24 separate points around the head), and adverse events. After recruitment, subjects kept diaries for four weeks prior to randomization, at which time they received either 200 U of BTX or matching placebo. Injection location was at the discretion of the injector. After injections, subjects kept diaries and were followed for 12 weeks. After the week-12 evaluation, patients were offered 200 of BTX (open label), and were similarly followed for another 12 weeks. **Results:** The mean days with headache of the 60 subjects (49 female, mean age 47 ± 11) was 23 ± 7 out of 30. There were no demographic differences between the drug and placebo groups (58 completed). At 12 weeks, headache free days had improved in the BTX group from weeks 8-12 ($p < 0.05$), and strongly tended to improve over the entire period of weeks 0-12, 33 ± 23 vs. 24 ± 16 days without HA, ($p = 0.07$). Subject global impressions ($p < 0.05$), subject change in headache impressions ($p < 0.005$), and investigator global impressions ($p < 0.001$) all improved in the BTX group compared to placebo. The number of abortive headache medications used only tended to improve (106 ± 76 vs. 135 ± 81, $p = 0.16$) favoring the BTX group, and palpation scores did not change. Adverse events were mild and did not differ between groups. At week 24, comparisons between the group that had received two BTX injections versus the group which received only one BTX injection showed that the twice injection group had fewer HA days over the 12 week period, 40 ± 26 vs. 26 ± 19, ($p < 0.05$). **Conclusion:** BTX may help CDH and appears to have a cumulative effect with subsequent injections.

INTRODUCTION

Chronic daily headache (CDH) is a heterogeneous disorder, generally defined by greater than 15 headache (HA) days per month, [1] which affects 3-5% of the population. [2,3] It is the most common headache seen in headache specialty clinics, [4] and has enormous medical and socio-economical ramifications. CDH patients also suffer from high rates of anxiety and mood disorders, which predict a more intractable course. [5,6] More than 90% of CDH patients initially reported episodic headaches. [7] Analgesic overuse is clearly associated with an evolution toward CDH, although the exact causal role is not clear. [8] The most common CDH subtypes are chronic tension headache (CTH) and chronic migraine (CM), however many patients report overlapping clinical features making definite segregation problematic.

Botulinum toxin A (BTX), Botox®, Allergan, inhibits endocytosis of neurotransmitters from the nerve terminal. The drug is most commonly used to reduce muscle contraction, which results from inhibition of acetylcholine release at the neuromuscular junction. In fact, only recently has inhibition of other neurotransmitters been explored for possible therapeutic mechanisms.

BTX has been reported to improve a variety of headache types. [9-20] Many of these trials, however suffer from methodological shortcomings including the lack of control groups, small sample sizes, and unsystematic data acquisition. We have, therefore designed a double blind, placebo controlled parallel design trial to assess the efficacy of BTX for CDH.

METHODS

Sixty patients, age 18-80, with headaches of more than 15 days per months were recruited from the Baylor College/Methodist Hospital Headache Clinic. Inclusion was not predicated on the suspected sub-type of CDH, but 19 were felt to have CM, 22 were felt to have CTH, and 19 had features of both.
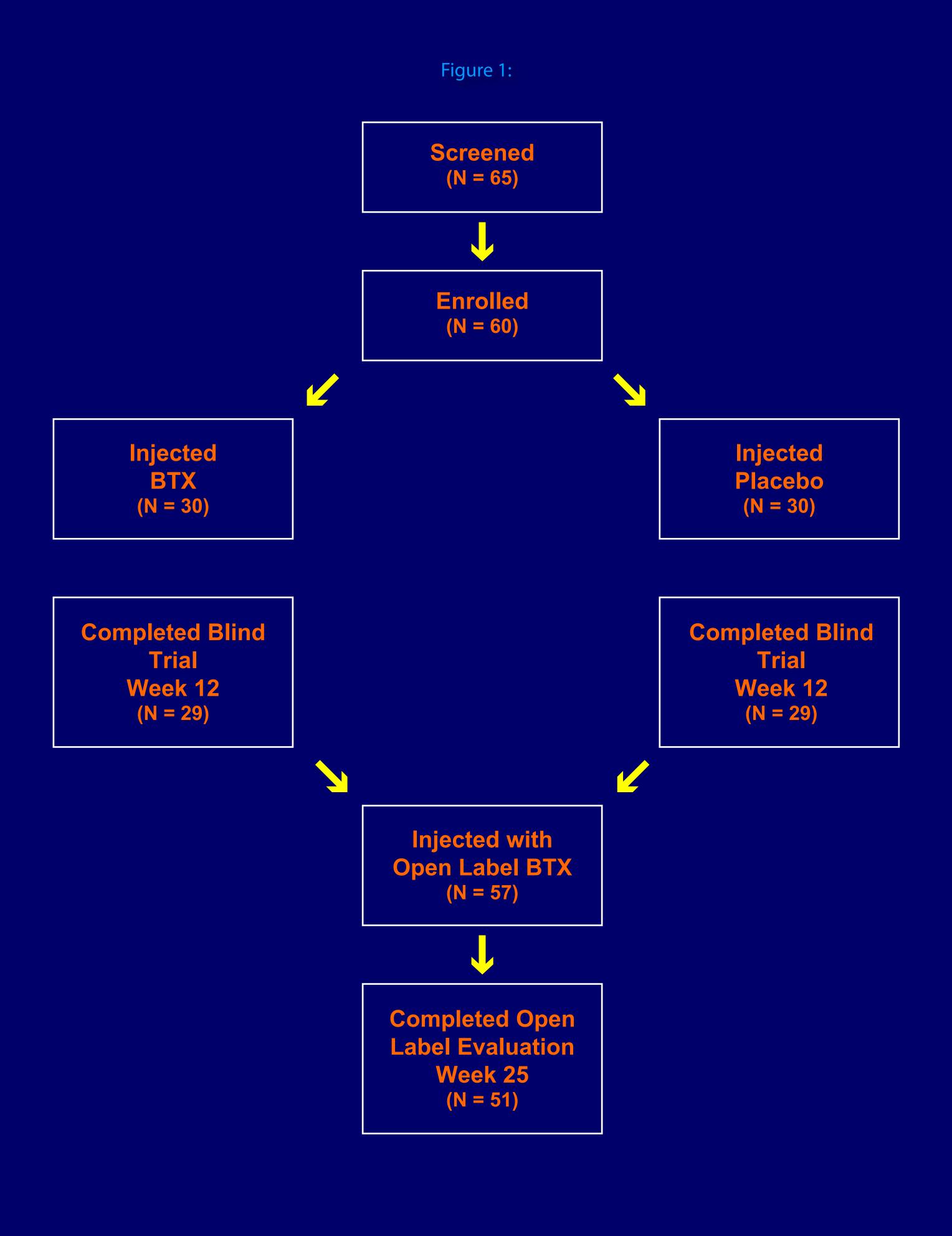
This was a double blind, placebo controlled, parallel design with a subsequent open label injection. The study was approved by the Baylor College of Medicine Internal Review Board, and informed consent was obtained in all patients. If subjects passed the screening questionnaire regarding headache frequency, they were enrolled, and then kept diaries of days with and without headaches. After four weeks, they returned to clinic and were randomized (1:1) to receive 200 U of BTX or matching placebo. The injection locations were at the discretion of the injecting physician (WO), but generally employed a "follow the pain" strategy. (Table 1) After four weeks, patients returned for their initial post-injection evaluation. After eight additional weeks they returned for the final blinded evaluation. All patients were then offered open label BTX injections. They again returned at four and twelve weeks after the second injection for identical assessments.

The primary efficacy point was headache diaries. Secondary efficacy points included global impressions, the use of abortive headache medications, palpation scores (rated 0-4 at 24 separate points around the head), the Beck Depression Inventory (BDI), [21] the Psychosocial Adjustment to Illness Scale (PAIS), [22] and adverse events. These were obtained at each clinic visit.

Statistical analysis of continuous variables included Student-T test. Dichotomous variables used Fisher Exact tests. For patients who did not complete the second 12-week assessment, we used a mean substitution intention to treat analysis.

Two stepwise regression models with backward deletion were then constructed to determine factors that correlated with initial post-injection improvement. The first compared headache free days during the pre-injection period (weeks -4-0) versus weeks 0-12 (blinded period) for those randomized to BTX. The second compared the pre-injection period (weeks -4-0) versus weeks 12-24 (open label period) for all subjects. Demographic variables included age, gender, headache type, initial palpation scores, and initial BDI scores. Technique variables included injection locations (primarily posterior vs. primarily anterior vs. masseter muscles), and initial randomization (for open label weeks 12-24 only).

RESULTS

The mean age of the 60 subjects (49 female) was 47 ± 11 years and the mean days with headache were 23 ± 7 out of 30. A single 16-year old female was included as a protocol violation due to her severe refractory CDH and her inability to receive injections off protocol. Five patients were eliminated at screening. Two subjects (one in each group) were lost to follow-up immediately after injections, and are not included in any data analysis. [Figure 1] There were no demographic or phenotypic differences between the drug and placebo groups. [Table 1]

Compared to placebo, headache free days improved in the BTX group from week 8-12 ($p < 0.05$, t-test), and strongly tended to improve over the entire period of weeks 0-12, 33 ± 23 vs. 24 ± 16, ($p = 0.07$). [Figure 2] Subject global ($p < 0.05$, Fisher exact test), subject change in headache impressions ($p < 0.005$), and investigator global impressions ($p < 0.001$) all improved in the BTX group compared to placebo. [Figure 3] The number of abortive headache medications used only tended to improve over the 12-week period in the BTX group, (106 ± 76 vs. 135 ± 81, $p = 0.16$). Palpation scores, the BDI, and PAIS scores did not change.

Adverse events were mild and did not differ between groups. Only a single patient with eyelid ptosis was thought to have a definite BTX related AE. Overall, 33 AE were reported in the drug group and 39 were reported in the placebo group. None of these were rated as serious or resulted in discontinuation.

Only one patient who completed the controlled trial elected not to receive open label injections. Seven patients, however, did not complete the entire subsequent 12-week open label evaluation within protocol because they did not faithfully complete headache diaries (3), started a new HA medication (3, including 1 who had BTX-A injected elsewhere), or moved (1). At week 24, comparisons between the group that had received two BTX injections (n = 26 completed) versus the group which received only one BTX injection (n = 25 completed) showed that the twice injected group had fewer HA days over the 12-week period, 40 ± 26 vs. 26 ± 19, ($p < 0.05$). [Figure 2]

In the demographic analysis of the original 30 subjects who were randomized to BTX (age, gender, headache type, palpation score, BDI), no predictors of superior response could be identified. However, when assessing the response at 12-24 weeks for all patients who received open-label injections, patients with muscle contraction sub-type of CDH ($p = 0.06$) and women ($p = 0.09$) tended to have more improvement.

In the technique analysis of the original 30 BTX recipients, subjects who received injections into the masseter (n = 9) did worse ($p < 0.05$). Masseter injections, however, no longer predicted a worse response when assessing the entire open label group. Those who received two BTX injections did better than those who only received one BTX injection ($p < 0.05$).
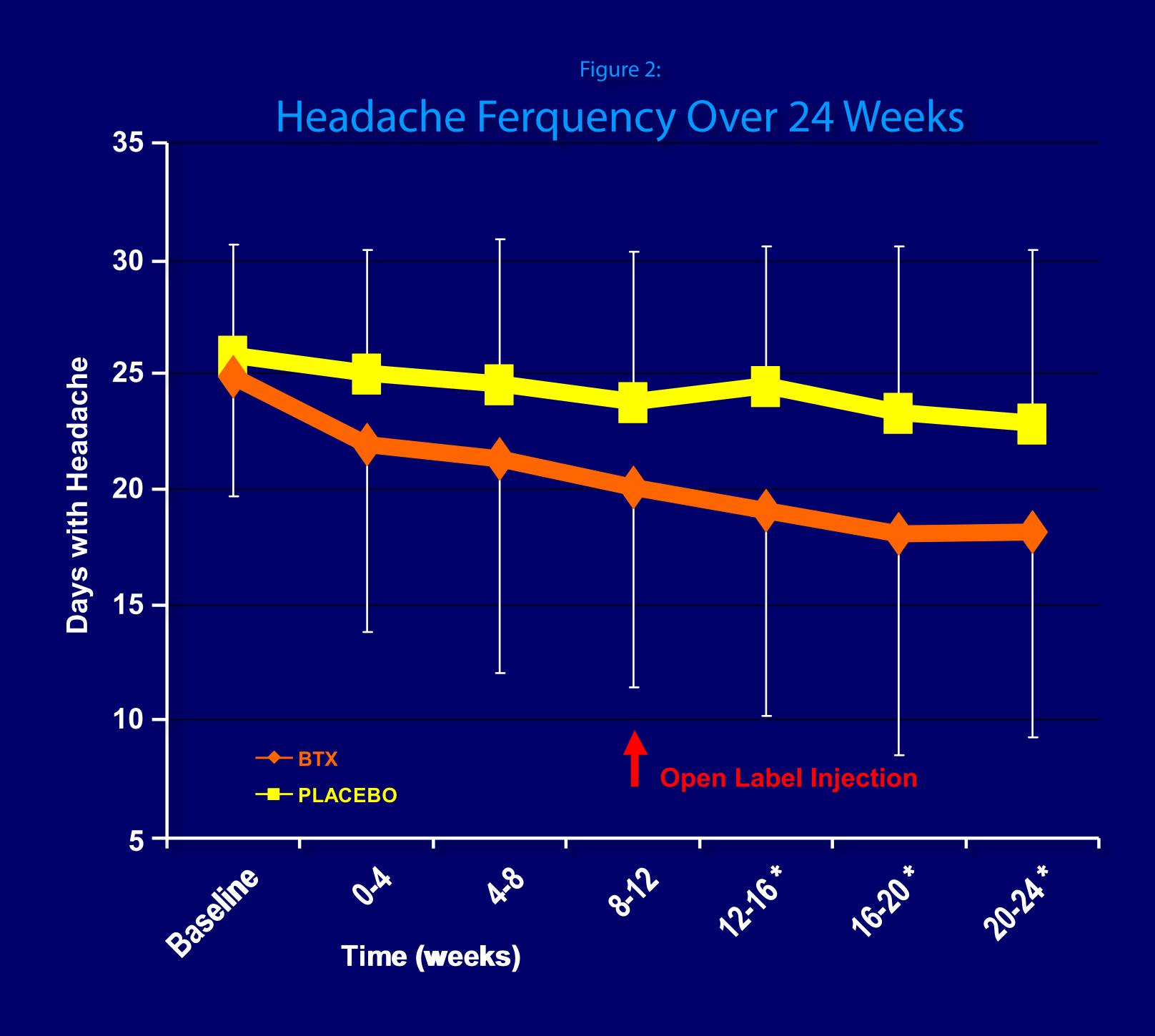
Figure 1:

Screened (N = 65) → Enrolled (N = 60) → Injected BTX (N = 30) / Injected Placebo (N = 30) → Completed Blind Trial Week 12 (N = 29) / Completed Blind Trial Week 12 (N = 29) → Injected with Open Label BTX (N = 57) → Completed Open Label Evaluation Week 25 (N = 51)
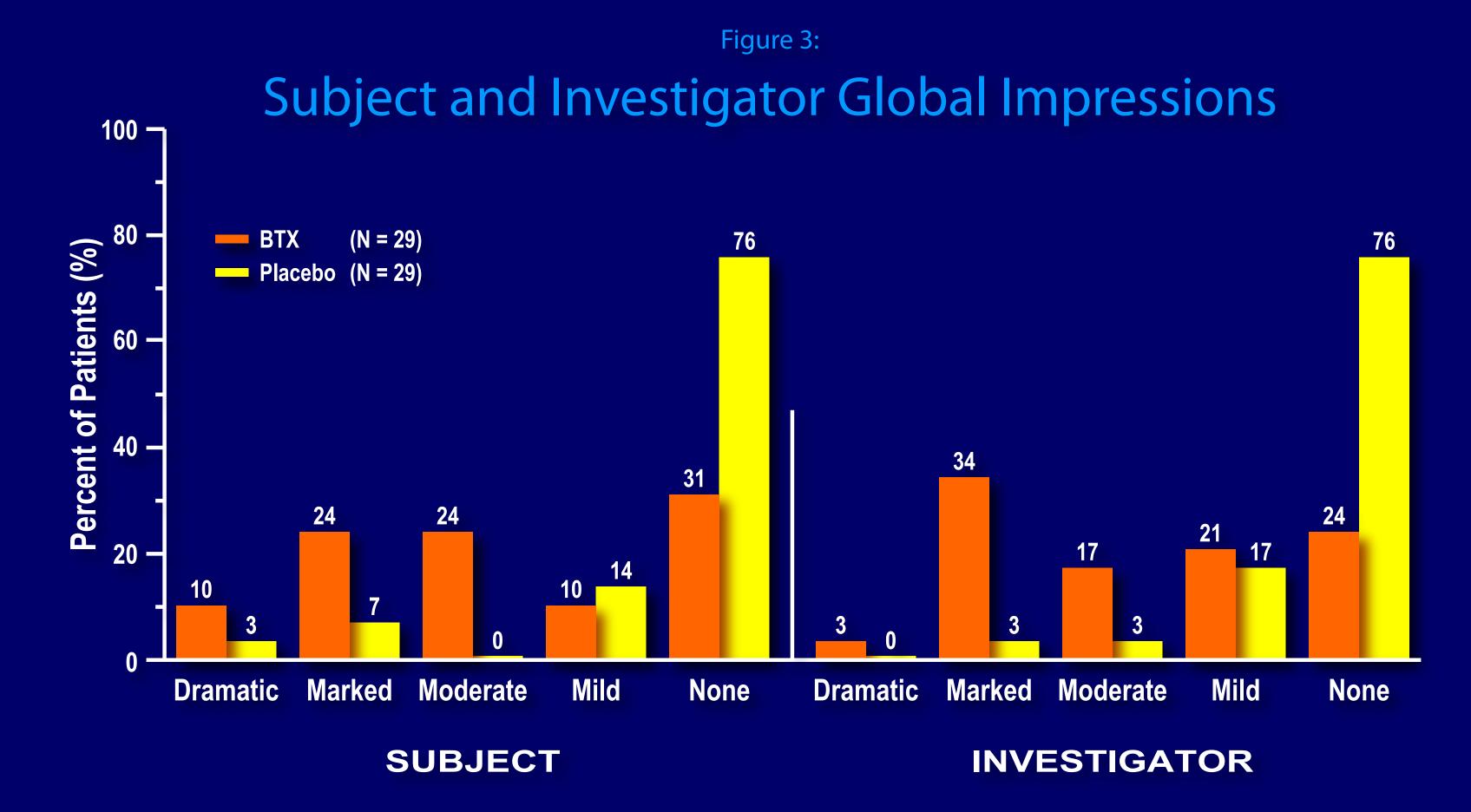
Table 1:
Patient Demographics and Pre-Injection Data

		BTX	Placebo
Sample Size		30	30
Age		46.3 ± 9.4	47.7 ± 12.7
Sex (male)		7	4
Days with Headache		24.8 ± 0.8	25.8 ± 0.9
Headache Type:	CDM	10	9
	CT	11	11
	Mixed	9	10
Palpation Score		17.1 ± 13.0	20.2 ± 12.3
BDI		3.3 ± 4.0	4.7 ± 4.8
PAIS		32.0 ± 23.2	34.6 ± 20.4
Prophylactic Medications		30 (n = 20)	37 (n = 20)
Abortive Medication Use (per month)		41.7 ± 24.4	49.0 ± 28.2
Dose to Anterior Muscles		79 ± 35	75 ± 32
Dose to Posterior Muscles		105 ± 47	106 ± 44
Dose to Masseter Muscles		60 ± 15 (n = 9)	76 ± 24 (n = 7)

CDM = chronic daily migraine, CT = chronic tension
BDI = Beck Depression Inventory, PAIS = Psychosocial Adjustment to Illness Scale

Figure 2:
Headache Ferquency Over 24 Weeks

Days with Headache vs. Time (weeks): Baseline, 0-4, 4-8, 8-12, 12-16*, 16-20*, 20-24*. Series: BTX, PLACEBO. Open Label Injection.

Figure 3:
Subject and Investigator Global Impressions

Percent of Patients (%) for BTX (N = 29) and Placebo (N = 29). SUBJECT: Dramatic, Marked, Moderate, Mild, None. INVESTIGATOR: Dramatic, Marked, Moderate, Mild, None.

DISCUSSION

Our findings suggest, but do not confirm, that BTX improves CDH. Adverse events were minimal. Interesting, subject global impressions robustly improved whereas HA diaries only strongly tended to improve, suggesting that unmeasured features may contribute to patient satisfaction. Finally, subjects randomized to BTX further improved after their second BTX injection, suggesting that multiple injections may be required to optimize results.

Although, not an a priori data assessment, we also noted a large number of patients who subjectively admitted to probable nocturnal bruxism, most of whom were not previously diagnosed. Self-report of bruxism is only moderately reliable, [23] and we did not specifically assess for bruxism via dental examination or polysomnographic studies. Bruxism is also common in the general population. Nevertheless, we feel that this association warrants further study, even though injection into the masseter did not seem to help these HA patients.

Unlike oral medications, results from BTX injections are technique dependent. We used a relatively high dose (200 U), highly concentrated solution (100 U/ml) and a "follow the pain" strategy without EMG guidance. A variety of doses and techniques are used to treat HA, but no data comparing optimal techniques for HA exist.

Our results generally support those of two other controlled trials of BTX-A for CTH. [19,24] Freund et al conducted a placebo controlled, parallel design study in 26 patients with chronic "cervicogenic" headache. Using 100 U diluted into 1 cc, they injected five cervical trigger points. At four weeks, BTX-A subjects reported less subjective pain using a visual analogue scale. Smuts et al reported a double blind, placebo controlled, parallel design trial of 37 subjects with CTH associated with disorders of pericranial muscles. They injected posterior and temporalis muscles with 100 U BTX-A in 2 ml. Headache severity scores and days without headache improved on drug during a 3-month post-injection period. Schmitt et al showed mixed results in a 60 patient, controlled parallel trial injecting only 20 U of BTX into frontal and temporal muscles in patients with CTH. [25] In contrast, Gobel et al, in a 20 patient parallel study, employing 10 U into the frontalis, 10 U into the auricularis, and 20 U into the splenius capiti, did not demonstrate reduced number of HA days in CTH. [26]

Consistent with our results, long term open label data suggests that CDH patients report further improvement with multiple subsequent injections. [27] The mechanisms by which this occurs are speculative, but may involve gradual effects on CNS sensitization.

The pathophysiology of CDH is not well understood and is likely multi-factorial. Patients with CTH demonstrate increased muscle hardness, [28] decreased threshold to pain stimuli, [29] and CNS sensitization, possibly associated with nitric oxide. [30] Genetic factors may also predispose to CTH. [31] Direct physiological comparisons between CTH and CM have not been reported.

The mechanism by which BTX improves HA pain is not known. A variety of neuropeptides that are affected by BTX-A, including substance-P and calcitonin gene related peptide (CGRP) [32-34] are also implicated in headache. [35-38] In fact, triptin 5-HT(1B/1D) agonists may improve migraine pain using similar, although less focal, mechanisms as BTX. [39] Relaxation of muscle tightness may also contribute, especially since our patients with CTH tended to improve more than those with CM.

Potential weaknesses of this study include non-optimized injection technique and dose. Our subjects were seen at a tertiary referral center and may represent a more refractory population. Purely subjective outcome measures are also an intrinsic weakness to all HA studies. Finally, injection of normal saline and "dry needle" injections have been shown to improve headache. [40] Therefore, BTX studies are actually compared against a potentially active treatment, which may account for some of the "placebo" response. Nevertheless, we feel that our result warrant larger controlled trials for CDH.

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