

Nelson Barrientos
Pedro Chana

Botulinum toxin type A in prophylactic treatment of migraine headaches: a preliminary study

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N. Barrientos (✉) • P. Chana
Dipreca Hospital,
Av Vital Apoquindo 1200,
Santiago, Chile
e-mail: nbu@adsl.tie.cl
Tel.: +562-2734015
Fax: +562-2751842

Abstract The purpose of this study was to determine the safety and efficacy of botulinum toxin type A (BOTOX; Allergan, Irvine, USA) in migraine prophylaxis. We performed a double-blind, randomized, 90-day placebo-controlled study that enrolled 30 adult migraineurs. Patients received 50 units botulinum toxin type A (n=15) or placebo (n=15). Outcome measures were monthly frequency and duration of migraine attacks and the number of severe attacks. Botulinum toxin type A produced significantly greater reductions in the frequency of migraine attacks

of any severity at Day 90 (-3.14 vs. -0.53; $p<0.05$) and in the frequency of severe migraine attacks at Days 60 (-1.4 vs. -0.54; $p<0.05$) and 90 (-1.8 vs. -0.20; $p<0.02$). One patient in the botulinum toxin type A group experienced mild, transient frontalis muscle weakness lasting approximately 30 days. Botulinum toxin type A injections were well tolerated and provided effective migraine prophylaxis in these patients.

Key words Migraine • Botulinum toxin type A • Prophylaxis • Double blind • Placebo control

Introduction

It is estimated that approximately 18% of women and 6% of men in the US suffer from migraine headache [1, 2], and an increasing number of migraine sufferers receive a medical diagnosis [3]. The annual cost of lost productivity to the US economy attributable to migraine has been estimated at US \$13 billion [4].

The goals of long-term treatment of migraine include reducing the frequency and severity of attacks and the use of acute pharmacotherapies to minimize the risk of adverse events and exacerbation of headache [5]. Most experts recommend that abortive medications such as triptans, analgesics, and non-steroidal anti-inflammatory drugs (NSAIDs) be used intermittently, rather than prophylactically. Many traditional prophylactic drugs are of limited efficacy or are poorly tolerated by some patients. In addition, many patients prefer to avoid the use of systemically acting medications that may cause adverse events or drug interactions.

Botulinum toxin type A, a potent neurotoxin produced by the bacterium *Clostridium botulinum*, inhibits acetylcholine release at neuromuscular junctions, causes reversible chemodenervation, and results in muscle relaxation and decreased tone lasting approximately 3–4 months [6]. It has been used successfully in the treatment of disorders characterized by increased muscle tone or hyperactivity such as cervical dystonia, blepharospasm, and spasticity [7–12]. Botulinum toxin type A may influence pain modulation mechanisms distinct from its muscle-relaxing effects through substance P from trigeminal nerve ends [13]. Substance P is a powerful mediator of neurogenic inflammation implicated in migraine pathogenesis [14].

Interest in botulinum toxin type A as a prophylactic treatment for migraine began with studies that were originally investigating botulinum toxin type A as a treatment for hyperfunctional facial lines but that also reported relief of migraine symptoms [15].

Subsequently, Binder et al. [16] conducted an open-label study involving 106 patients who sought treatment with bot-

ulinum toxin type A (BOTOX; Allergan, Irvine, USA). Of the 77 true migraine patients who received botulinum toxin type A, 51% reported a complete response (symptoms elimination) and 38% reported a partial response ($\geq 50\%$ decrease in headache frequency or severity).

A randomized, double-blind, placebo-controlled study was conducted by Silberstein et al. [17] in 123 migraine patients. Single administrations of placebo or botulinum toxin type A (25 or 75 U) were injected into multiple sites of pericranial muscles. Compared with patients in the vehicle-treatment group, patients in the 25-U botulinum toxin type A-treatment group showed significantly greater reduction in moderate-to-severe migraine frequency at month 2 ($p < 0.01$) and at month 3 ($p < 0.05$), and in the number of migraines of any severity at month 3 ($p = 0.01$).

While previous studies reported improvements in headache symptoms with botulinum toxin type A treatment, definitive data identifying the most effective injection protocol have not emerged. The aim of this randomized, placebo-controlled, double-blind study was to evaluate the efficacy and safety of a 50-U dose of botulinum toxin type A, administered intramuscularly in the face and neck regions, for the prophylactic treatment of migraine.

Patients and methods

Patients

Forty-nine patients were screened to identify 30 individuals between the ages of 18 and 65 years who met the entry criteria. Nineteen patients

were not included due to abuse of ergotamines, analgesics, or caffeine. Eligible patients had at least a 1-year history of episodic migraine, with or without aura, as defined by the criteria of the International Headache Society (IHS). All patients were followed for 3 months. Patients were ambulatory and capable of recording details of their headache condition as well as any adverse events or medications required for acute treatment of attacks. All patients provided informed, written consent after the study procedures had been carefully explained.

Exclusion criteria included having more than 15 headaches per month; a history of complicated migraine (with aura); previous treatment with botulinum toxin of any serotype; clinical evidence, which, in the opinion of the investigator, indicated substance abuse, including overuse of analgesics and migraine treatments; and current prophylactic treatment for migraine. Female patients who were pregnant or lactating were excluded as were those with any condition, which, in the opinion of the investigator, could compromise the results of the study.

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

Study design

Eligible patients were randomized on a 1:1 basis to either a total dose of 50 U (50 U/ml) of botulinum toxin type A (BOTOX) or placebo in this double-blind study.

Botulinum toxin type A or placebo was administered pericranially by intramuscular injection at 15 sites in 6 locations at the front and back of the head and neck as follows: temporalis, 10 U total at 2 sites; frontalis, 10 U total at 4 sites; glabellar, 8 U total at 4 sites; procerus, 2 U at 1 site; trapezius, 10 U total at 2 sites; splenius capitis, 10 U total at 2 sites. The position of each injection site is shown in Fig. 1.

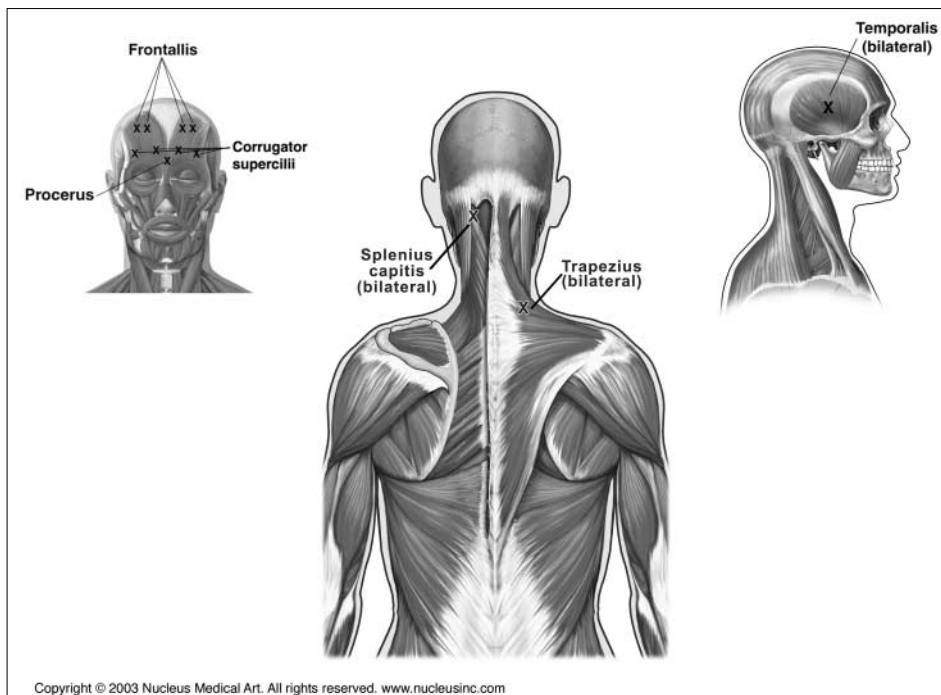


Fig. 1 Locations of botulinum toxin type A injection sites. (Reproduced from Nucleus Medical Art with permission)

Patients received a general physical and neurologic examination at baseline and at all subsequent visits. Following their injection visit (Day 0), patients were assessed at monthly intervals (Days 30, 60, and 90), and their diary entries were reviewed by the investigator.

Efficacy and safety assessments

Primary treatment efficacy outcomes included the frequency (number per month) of migraine attacks, the frequency of severe migraine attacks, and the duration (number of hours) of migraine attacks. Secondary treatment outcomes included the need for acute migraine treatments (number of NSAID or triptan tablets per month), the number of migraine attacks with nausea, and the effectiveness of treatment scored on the 6-point global effectiveness evaluations scale (1, very large improvement; 2, noticeable improvement; 3, some improvement; 4, very slight improvement; 5, no change; and 6, slight deterioration).

Patients were monitored throughout the study period for the incidence and severity of any adverse effects. Investigators probed for adverse events by direct questioning and examination of patients' diaries at all postinjection visits.

Statistical analyses

All analyses were performed on the intent-to-treat population. The comparisons of migraine outcome measures with baseline values were analyzed using the Mann-Whitney U test for each treatment group. Comparisons between the botulinum toxin type A and placebo groups for baseline demographic characteristics and migraine outcome measures (frequency, duration, and number of moderate and severe attacks, and the number of acute medications used) were performed also using the Mann-Whitney U test. Reduction over time of the frequency and duration of attacks and the use of acute medication was analyzed using Friedman's test.

Results

Thirty patients were randomized to treatment: 15 to botulinum toxin type A and 15 to placebo. All patients complet-

ed the study. Baseline demographic characteristics showed no significant differences between the patient groups (Table 1). Baseline migraine assessments were also comparable between the 2 groups in the 3 months prior to enrollment (Table 1).

A significantly greater reduction in the frequency of migraine attacks of any severity occurred with the use of botulinum toxin type A compared with placebo at Day 90 (-3.14 vs. -0.53, respectively; $p < 0.05$) (Fig. 2). There was a significant decrease in the frequency of migraine attacks for botulinum toxin type A patients postinjection relative to the baseline amount (5.7) at Days 30 (-2.1; $p < 0.02$), 60 (-2.5; $p < 0.02$), and 90 (-3.14; $p < 0.01$). In contrast, there were no significant decreases from baseline to any time point in the frequency of migraine attacks in placebo patients. Over the 90-day study period, there was a significant reduction in the frequency of attacks in the botulinum toxin type A group ($p < 0.001$), whereas no significant reduction was seen in the placebo group.

Significantly greater reductions in the frequency of severe migraine attacks were observed with botulinum toxin type A compared with placebo at Days 60 (-1.4 vs. -0.54; $p < 0.05$) and 90 (-1.8 vs. -0.2; $p < 0.02$) (Fig. 3). There were significant reductions in the frequency of severe migraine attacks relative to baseline (2.13) for the botulinum toxin type A group at Days 30 (-1.2; $p < 0.05$), 60 (-1.4; $p < 0.01$), and 90 (-1.8; $p < 0.02$). There was no significant reduction in the frequency of severe migraine attacks relative to the baseline amount for the placebo group at any time point.

Significantly less use of acute migraine treatments per month was associated with botulinum toxin type A compared with placebo at Days 60 (3.27 vs. 5.53; $p < 0.05$) and 90 (1.73 vs. 5.60; $p < 0.001$) (Fig. 4). The use of acute migraine treatments (NSAIDs and triptans) per month, as compared with usage at baseline (6.40), was also significantly reduced ($p < 0.001$) in the botulinum toxin type A group at Days 30 (-3.47), 60 (-3.13), and 90 (-4.67). Furthermore, acute medication use decreased significantly over time in the botulinum toxin type A group ($p < 0.001$), but not in the placebo group (Fig. 4).

Botulinum toxin type A treatment significantly reduced the duration (hours) of migraine attacks experienced rela-

Table 1 Patient demographics and baseline migraine measures. Values are means unless otherwise indicated. No difference between groups was significant (Mann-Whitney U test)

	Placebo group (n=15)	Botulinum toxin group (n=15)
Women, n (%)	12 (80)	12 (80)
Age, years	39.6	42.5
History of migraine, years	12.7	18.5
Frequency of migraine attacks, n/month	4.5	5.7
Duration of attacks, h	16.3	12.8
Frequency of taking acute treatment, n/month	5.2	6.4

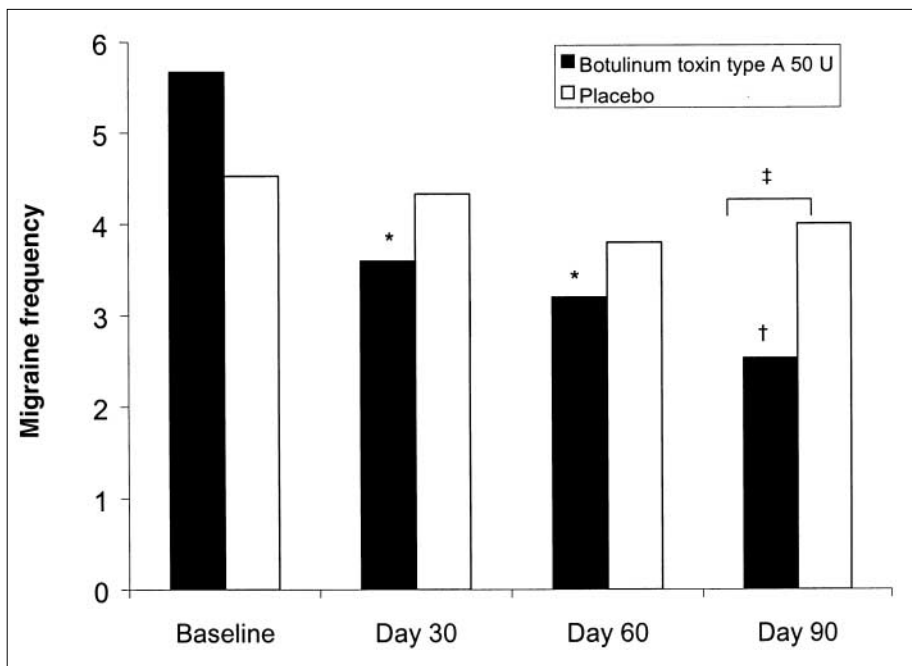


Fig. 2 Frequency of migraine attacks of any severity (mean number per month). * $p < 0.02$, † $p < 0.01$ vs. baseline, ‡ $p < 0.05$ botulinum toxin type A vs. placebo

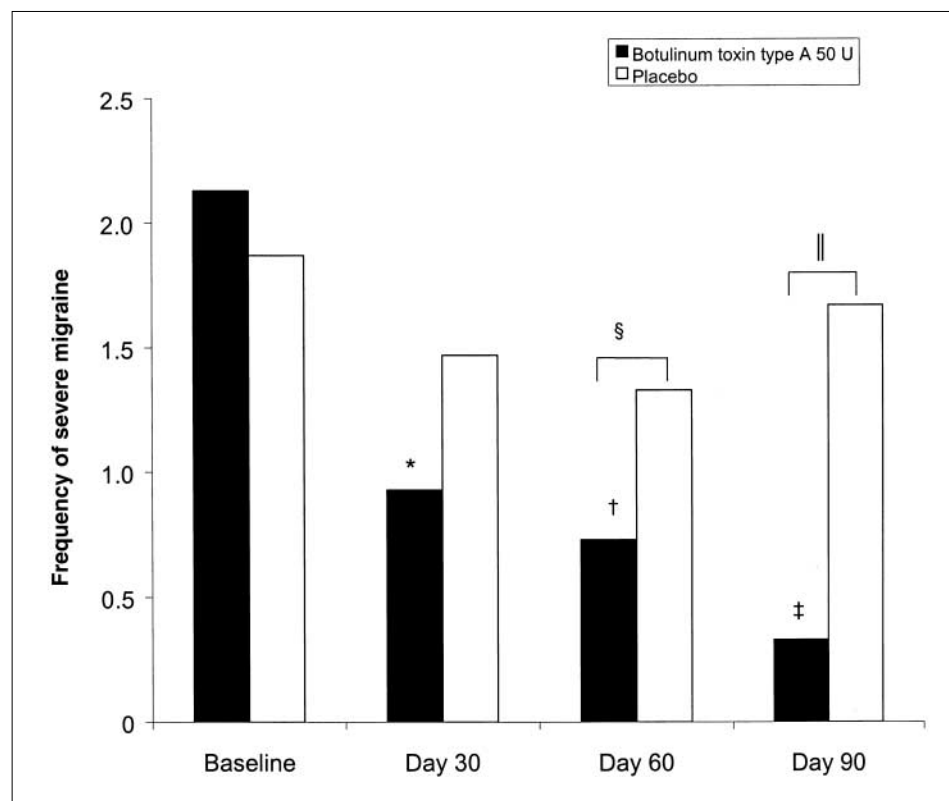


Fig. 3 Frequency of severe migraine attacks (mean number per month). * $p < 0.05$, † $p < 0.01$, ‡ $p < 0.02$ vs. baseline; § $p < 0.05$, || $p < 0.02$ botulinum toxin type A vs. placebo

tive to the baseline amount (12.8) at Days 30 (7.53; $p < 0.05$), 60 (5.80; $p < 0.02$), and 90 (3.13; $p < 0.01$), reaching a 75% reduction. The decrease in the duration of attacks over time was statistically significant for patients

receiving botulinum toxin type A treatment ($p < 0.001$), but not for those receiving placebo.

The mean number of migraine attacks with nausea was significantly reduced ($p < 0.005$) from baseline (3.3) after

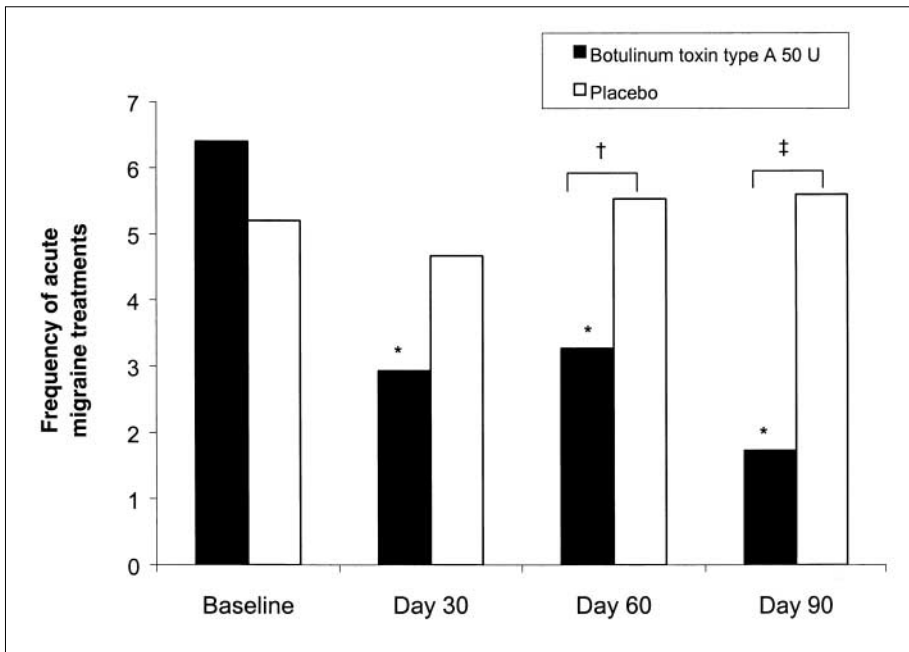


Fig. 4 Frequency of acute migraine treatment (mean number of tablets per month). * $p < 0.01$ vs. baseline; † $p < 0.05$, ‡ $p < 0.001$ botulinum toxin type A vs. placebo

active treatment at Days 30 (0.9), 60 (0.9), and 90 (0.8), but not after the use of placebo.

Global effectiveness evaluations scale results for both patients' and investigators' evaluations indicated significantly greater improvements from baseline for those receiving botulinum toxin type A than for those receiving placebo. At the end of the study, mean patient evaluation scores were 2.00 in the botulinum toxin type A group compared with 4.13 in the placebo group ($p < 0.001$). Mean values of the investigator assessments were 2.33 in the botulinum toxin type A group compared with 4.47 in the placebo group ($p < 0.001$).

Botulinum toxin type A treatment was well tolerated. One patient in the botulinum toxin type A group experienced transient frontalis muscle asymmetry lasting approximately 30 days.

Discussion

This study supports the effectiveness of a single treatment of 50 U botulinum toxin type A administered by intramuscular pericranial injections for the prophylaxis of migraine. The beneficial effects shown in this study of botulinum toxin type A treatment compared with placebo replicate the results of earlier controlled trials [17, 18]. The improvements associated with botulinum toxin type A treatment continued through 90 days, suggesting continued improvement after that time.

Our conclusions are based on the findings from physical neurologic examinations and a review of the headache

diaries at each assessment, but we also included findings from a patient- and investigator-rated global effectiveness evaluations scale. This scale, while not yet validated, may provide a useful qualitative means for assessing treatment response from the viewpoints of both patients and investigators. Results were reported for all measures over the 3-month study duration, although the data suggest efficacy extended beyond this time point.

The reduced pain associated with botulinum toxin type A treatment may result in significant cost savings if the use of acute medication is reduced. Since migraine illness impacts pharmacoeconomic costs estimated to amount to billions of dollars every year to US patients [4], the prophylactic use of botulinum toxin type A could potentially offset substantial costs for healthcare and lost labor [19]. Overall, in our study, the benefits of botulinum toxin type A treatment were progressive – which is consistent with others' findings [16, 17]. Because the benefits of botulinum toxin type A treatment appear to be progressive, more research should be conducted regarding the duration of benefits for episodic migraine.

In addition to its muscle-relaxant properties, botulinum toxin type A is an exocytotic inhibitor and may have antinociceptive properties through some as-yet-undefined effect on the sensory system [20]. Results of studies performed to date suggest the effectiveness of botulinum toxin type A in treating migraine may result from a combination of its muscle-relaxant and antinociceptive properties.

The highly focal nature of botulinum toxin type A injections and the multiple modes of action of this agent suggest that targeted distribution of the toxin around the face, the back of the head, and the neck musculature offers the great-

est potential for effective intervention in migraine. For patients predisposed to migraine attacks, botulinum toxin type A may represent an important longer-term therapeutic advance over current prophylactic treatments.

Furthermore, results from this and other studies indicate botulinum toxin type A injections are well tolerated [16, 17, 21]. The localized nature of botulinum toxin type A treatment avoids systemic exposure and minimizes the risk of adverse events as compared with acute oral medications.

We believe future studies should follow patients for 4–6 months to properly define the time course of 1 treatment session, or for up to 1 year to measure the effect of multiple treatment sessions. Further investigation of this area using larger randomized, placebo-controlled studies to confirm the utility of more injection sites for treating migraine is warranted.

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