Brief Communication

Botulinum Neurotoxin Type A in the Preventive Treatment of Refractory Headache: A Review of 100 Consecutive Cases

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Objectives.—To review the efficacy of botulinum neurotoxin type A (BoNT-A) in the preventive treatment of refractory headache.

Background.—Even after receiving expert care, some patients with refractory headache continue to have high disability and persistent headaches.

Methods.—Clinical records and headache calendars of 100 patients fulfilling the following inclusion criteria were reviewed: (1) age from 18 to 65 years; (2) primary headache with previous failure of at least four preventive treatments; and (3) have received BoNT-A and have been followed for at least 6 months after the BoNT-A injections. BoNT-A (100 units) was diluted in 4-cc normal saline. The muscles injected included some or all of the following: frontalis, temporalis, corrugator, procerus, occipitalis, semispinalis, splenius capitis, trapezius, cervical paraspinalis, and sternocleidomastoid. Migraine-related disability was assessed using the Migraine Disability Assessment (MIDAS) questionnaire.

Results.—There was a statistically significant reduction of the frequency of headache days 1 month after BoNT-A was administered (14.2 vs 28.2 days at the baseline, $P < .001$), which was maintained through the 3 months of study; similarly, a significant reduction in the headache index (22.3 vs 40.3, $P < .001$) and number of severe days with headache per month (2.6 vs 7.4, $P < .001$) were found at 1 month and maintained through the 3 months of study. MIDAS scores were reduced from 34.5 at baseline to 15.9 at 3 months ($P < .001$). A similar pattern was found in those overusing versus nonoverusing acute medication, though the response was more dramatic in the nonoverusing subgroup.

Conclusion.—BoNT-A may play a role in the preventive treatment of refractory headache. A significant number of patients showed decrease in clinically important measurements of their headaches as well as reduced headache-related disability with this treatment. Prospective, controlled studies must be considered for severely disabled, refractory patients.

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Headache is a heterogeneous condition that results in a spectrum of disability within and among different individuals.[1] Headache disorders account for one in five outpatient visits to neurologists' offices in the United States.[2,3] Many of these patients have refractory headaches, announcing at the first consultation that they have already tried everything to treat their headaches and nothing has worked.[4]

The treatment of refractory headaches often poses a major challenge for the clinician. It requires a multidisciplinary approach, employing behavioral medicine techniques, daily preventive and appropriate acute-care medications, and withdrawal when appropriate of the acute-care medication being overused. To a great extent, ongoing treatment of refractory headache is based on the use of daily preventive medications, singly or in combination. Even after

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receiving expert care, a significant percentage of these patients continues to have persistent and refractory headaches.[5-7]

During the initial clinical trials of botulinum toxin type A (BoNT-A) for the treatment of wrinkles, Binder et al[8] noted that some patients also reported improvement in their headaches. Open and controlled trials investigated the efficacy of BoNT-A in the treatment of episodic migraine, chronic migraine, cluster headaches, and other forms of headache.[8,9] In a double-blind, vehicle-controlled study, Silberstein et al[10] reported that 25 units of BoNT-A, but not 75 units, injected pericranially significantly reduced the frequency and severity of attacks when compared with the vehicle.

The aim of this study was to retrospectively review the efficacy of BoNT-A in the preventive treatment of 100 patients with headaches refractory to many other standard preventive therapies, and to determine the effects of BoNT-A on disability in patients with refractory headaches.

METHODS

This study was performed at a headache clinic. We reviewed the clinical records and headache calendars (diaries) of 100 consecutive patients fulfilling the following inclusion criteria:

1. Age ranging from 18 to 65 years.
2. Primary headache with previous failure of at least four adequate courses of preventive treatments.
3. Use of BoNT-A with follow-up of at least 6 months after the BoNT-A injections.
4. On a stable dose of other preventive medication in the last 2 months.

Patients with incomplete records were excluded.

A total of 100 units of BoNT-A were diluted with normal saline to a concentration of 25 U/mL; muscles injected included some or all of the following: frontalis, temporalis, corrugator, procerus, occipitalis, semispinalis, splenius capitis, trapezius, cervical paraspinalis, and sternocleidomastoid. Fixed-site injections were performed in frontalis, and temporalis muscles bilaterally. A follow-the-pain approach was followed in the other muscles, but all were injected bilaterally.

Data were gathered prospectively by headache calendars (diaries). After the analysis of records and headache calendars, relevant information was transferred to a standardized form. The headaches were classified according the International Headache Society (IHS) criteria.[10] In patients with a headache frequency >15 days per month, the headaches were classified both according to the IHS and the criteria proposed by Silberstein and Lipton for chronic daily headaches (CDH).[11] We followed the revised IHS criteria to classify patients with medication overuse.[12]

Migraine-related disability was assessed with the Migraine Disability Assessment (MIDAS) questionnaire. The MIDAS questionnaire captures the information on disability in terms of missed days of paid word (or school), household work (chores), and nonwork time. All questions were asked about either days of missed activity (absenteeism) or days where productivity was reduced by at least at half (presenteeism). If productivity is decreased to 50% or below, the day is considered missed. The MIDAS score is derived as the sum of all days on which the patient suffered at least 50% disability at work, home, school, or recreational activities. The 4-point grading system for the MIDAS questionnaire is as follows: Grade I (scores ranging from 0 to 5) = little or no disability; Grade II (scores ranging from 6 to 10) = mild disability; Grade III (scores ranging from 11 to 20) = moderate disability; and Grade IV (21 or greater) = severe disability.

We analyzed the following endpoints, derived from the headache calendars and from the MIDAS questionnaire:

1. Frequency of headaches.
2. Intensity of pain (measured on a 4-point scale where 0 is no pain and 3 is severe pain).
3. Number of days with severe headache.
4. Headache index (frequency × intensity).
5. Number of pain-free days per month.
6. MIDAS scores.

Adverse events were defined as any untoward medical occurrence in a subject, temporally associated with the use of BoNT-A whether or not it is thought to be due to the medication.

Endpoints were measured in the month before BoNT-A injection (baseline) and monthly in the following 3 months. The MIDAS questionnaire was applied at baseline and 3 months after BoNT-A injections. Descriptive statistics were applied. The assumption was that the values were sampled from Gaussian distributions and tested using the Kolmogorov-Smirnov normality test. Matched comparisons in nonparametric distributions were performed using the Friedman test with post-test. Nonmatched comparisons in nonparametric distributions were performed using the Kruskal-Wallis test with post-test.

RESULTS

We reviewed the records of 118 patients receiving BoNT-A, to identify 100 subjects with complete records and satisfying the inclusion criteria.

Demographics and Diagnosis.—Our sample consisted of 100 subjects, 80 (80%) females. Age ranged from 18 to 64 years old, with a mean of 43.7 years (SD = 7.8). All were followed at least 6 months after receiving BoNT-A.

Table 1 exposes the diagnoses according to the IHS classification.[12] Migraine was the diagnosis in 21% of the subjects and chronic post-traumatic headache in 8%. The vast majority of the patients had CDH. According to the criteria proposed by Silberstein and Lipton, 65% had transformed migraine with medication overuse and 15% had transformed migraine without medication overuse.[11] According to the IHS, most of these patients with very frequent headaches had migraine plus chronic tension-type headache and medication overuse.

Table 1.—Diagnosis According the International Headache Society Classification

Diagnosis	n (%)
Migraine without aura	18 (18)
Migraine with aura	3 (3)
Migraine without aura + chronic tension-type headache	15 (15)
Migraine without aura + chronic tension-type headache + medication overuse (headache attributed to chronic exposure of substance)	62 (62)
Migraine without aura + migraine with aura + chronic tension-type headache + medication overuse (headache attributed to chronic exposure of substance)	3 (3)
Chronic post-traumatic headache	8 (8)

Medication Use.—The number of preventive drugs tried before inclusion in the BoNT-A study ranged from 4 to 22 (average of 12), including those they were on at the time of first injection.

At baseline, 65 (65%) patients were overusing acute-care medications, despite previous attempts at detoxification. One month after BoNT-A injections, 61 (61%, $P = .66$, two-sided χ^2) were overusing medications. This lack of change in medication overuse persisted at 2 months post injection, with 55 (55%, $P = .19$) overusing. However, by 3 months post-BoNT-A injection, 47 of 100 were overusing, which represented a significant drop (47%, $P = .01$ compared to the baseline).

Headache Frequency.—Figure 1 compares the frequency of headache at baseline and after BoNT-A, in those subjects who were overusing acute medications, in nonoverusers, and overall. Overall, a statistically significant reduction of headache frequency was obtained in 1 month (14.2 vs 25.2 at the baseline, $P < .001$), and maintained throughout the 3 months of study. The frequency at baseline was lower in the overusers group and the response was not as dramatic in the first month in this group, but similar patterns of improvement were found in overusers and nonoverusers (Figure 1).

The mean number of *severe* attacks per month is presented in Figure 2. Overall, a significant reduction, compared to baseline, was obtained in 1 month (5.1 vs 8.1 at the baseline, $P < .01$), and maintained throughout the 3 months of the study. Again, the response was not as dramatic in the first month in the overuser group, but similar patterns of improvement were found.

Figure 3 displays the headache index. Overall and by subgroups of overusers and nonoverusers, a statistically significant reduction of the headache index was obtained at 1 month and maintained throughout the duration of the study.

Migraine-Related Disability.—The MIDAS scores, overall and for each question, before and after BoNT-A injections are displayed in Table 2. Overall,

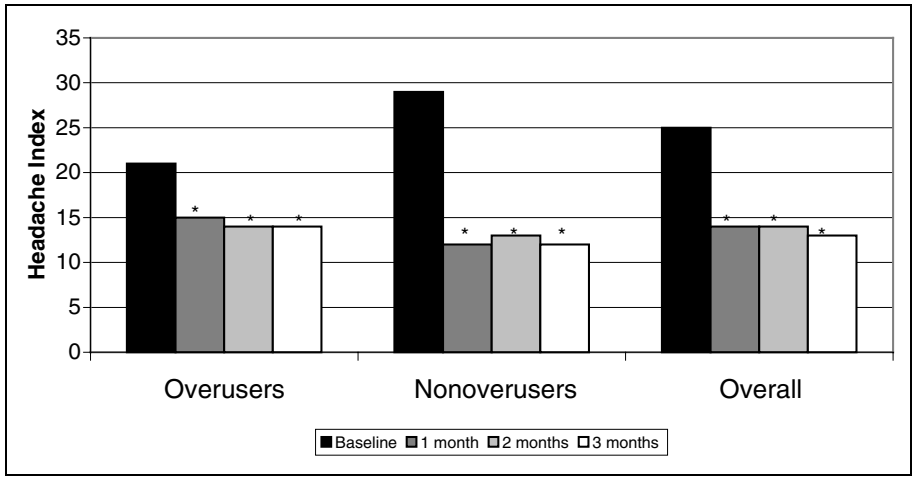

Fig 1.—Comparison of the frequency of pain at baseline and after botulinum toxin type A. *$P < .01$ versus baseline.

MIDAS scores were reduced from 34.5 at baseline to 15.9 at 3 months ($P < .001$).

In a 3-month period, BoNT-A reduced the number of days missed at work or school (2.4 vs 0.8, $P < .001$), number of days with reduced productivity at work or school because of the headache (9.1 vs 6.1, $P < .05$), number of housework days missed (7.2 vs 2.1, $P < .001$), number of days with reduced productivity doing housework (7 vs 3.5, $P < .001$), and days of social activity missed (7 vs 3.1, $P < .05$). According to the MIDAS questionnaire, the only domain where the differences were not significant was intensity of headache (8.2 vs 7.1 on a 10-point scale).

Adverse Events.—No patients were intolerant to BoNT-A in this study. A total of 19 (19%) patients reported side effects: 14% had pain at the site of the injections; 13% reported local edema; and 1% reported tingling at the site of the injections. No ptosis or worsening of the headaches were noted.

COMMENTS

It is usually accepted that patients with refractory headaches have a biologically determined problem that has either been misdiagnosed or mistreated or is simply very difficult to treat.[4] Nonetheless, most patients with refractory headaches benefit to some

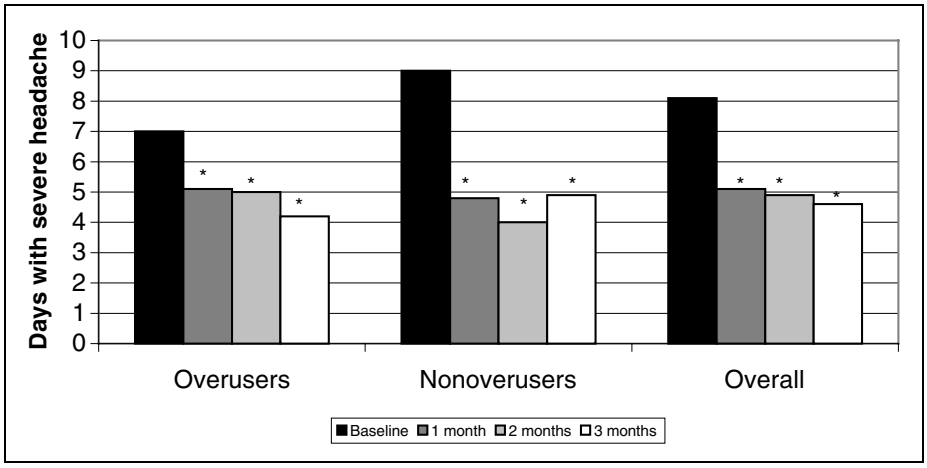

Fig 2.—Number of days with severe headache at baseline and after botulinum toxin type A. *$P < .01$ versus baseline.

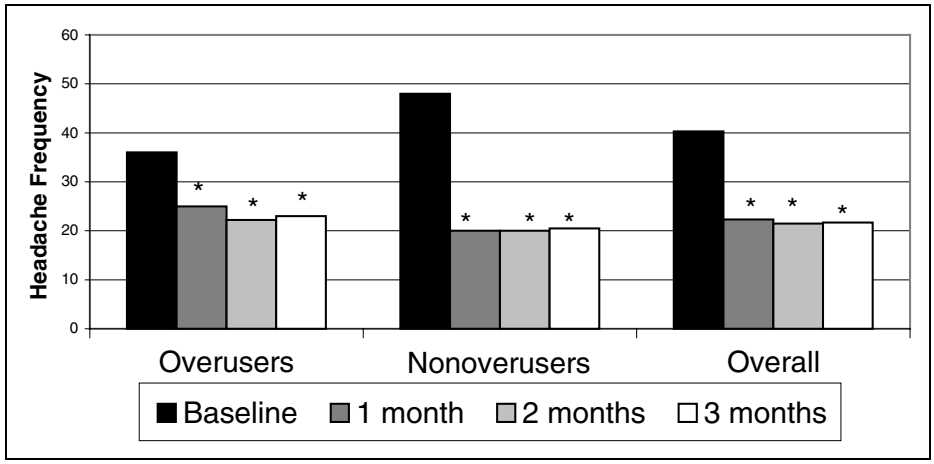

Fig 3.—Comparison of the headache index at baseline and after botulinum toxin type A. *$P < .01$ versus baseline.

degree from treatment at a tertiary headache center.[1,2] However, there is a subgroup of refractory headache patients that, despite optimized care, continues to manifest persistent, intractable headache, often overusing acute-care medications.

We present data from 100 refractory patients seen in a tertiary care headache center whom we decided to treat with BoNT-A. The study is uncontrolled. Therefore causality cannot be assigned to the intervention. Our data can be summarized as follows:

1. Treatment was associated with a decrease in the frequency of refractory headaches both in subjects overusing and not overusing acute-care medication, in the time period assessed.
2. Similarly, we verified a decrease in the number of severe headaches, in the time period assessed.
3. A subgroup of subjects overusing acute medication who received BoNT-A, stopped overusing medications by 3 months after treatment.
4. Treatment was associated with a decrease in the disability, in the time period assessed.
5. BoNT-A was well tolerated.

Table 2.—Comparison of the Disability Scores at Baseline and After Botulinum Toxin Type A

Question	Baseline	Three Months	*P* value
1. Days missed at work or school	2.3	0.8	<.001
2. Days with < 50% productivity at work or school	9.1	6.1	<.05
3. Housework days missed	7.2	2.1	<.001
4. Days with <50% productivity in housework	7	3.5	<.001
5. Days of social activity missed	7	3.1	<.05
(a) Days with headache per 3 months	33.5	12.1	<.001
(b) Intensity of headache	8.2	7.1	NS
MIDAS Score	34.5	15.9	<.001

The efficacy of BoNT-A in the prevention of migraine has been recently assessed.[14] There are few studies that have addressed the preventive treatment of refractory headaches as a distinctive subgroup of primary headaches. Most studies have assessed the efficacy of a particular drug in the treatment of CDH, which may or may not be refractory to the treatment.[13,14] For example, in an open-label trial, Mathew and Ali[15] assessed the possible benefits of sodium valproate in consecutive CDH patients who were refractory to multiple standard treatments. Fifty-five percent had some kind of response and 10% discontinued medication due to side effects. In other study, Shuaib et al[16] treated 37 patients with refractory migraine or CDH with topiramate (TPM) in an open-label study. Thirty percent had an excellent result and 30% had a good result, which suggests that TPM may be useful for CDH.

The prevention of CDH with BoNT-A has been studied recently. Ondo et al[17] showed that CDH sufferers who received BoNT-A had significantly fewer days with headache compared with those who received placebo. Miller and Denny[18] conducted a retrospective cohort analysis of 48 CDH sufferers treated with BoNT-A and concluded that most of them had good response. A recent study published as an abstract evaluated the role of BoNT-A in the treatment of intractable headache.[19] Patients had failed at least three preventive drugs; 49% presented good or better results after the first cycle of injections. Our data support this open study, which reported improvement in refractory headache sufferers after BoNT-A injections.

Several precautions must be taken when analyzing our results. First, this is a retrospective study, open-label analysis, neither placebo-controlled nor blinded. As in almost all initial studies that evaluate new possibly preventive treatments for headache, it is a preliminary open study. Second, only patients with very refractory headaches were included, which can significantly underestimate the potential results of the therapy in less recalcitrant patients. Third, some of the subjects stopped overusing acute-care medication during the study. Part of the benefits can, therefore, be due to analgesic discontinuation, rather than BoNT-A efficacy alone. The analysis of the subgroup that did not discontinue the medication during the study, however, showed the same pattern of benefit. Finally, side effects were self-reported, which may have underestimated their prevalence. Also, despite the assessment of tolerability, the safety of the utilization of BoNT-A was not evaluated by subsequent examinations.

The results of this study suggest that BoNT-A may be considered as a potential treatment for refractory headache, after our results are supported by prospective controlled studies.

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