

# Predicting Migraine Responsiveness to Botulinum Toxin Type A Injections

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**Background:** Botulinum toxin type A (BTX) is used prophylactically to reduce the frequency of migraine headaches, with inconsistent responses reported in the literature. The purpose of our study was to determine whether BTX injections at doses used for upper-face cosmetic purposes, which differ from doses typically used by headache specialists, could prevent imploding and ocular but not exploding migraines.

**Observations:** Study participants were recruited among patients who had received or were planning to receive BTX injections for upper-face cosmetic purposes but also reported having migraines. Among the 18 patients who

completed the study, most with imploding and ocular migraines experienced a significant reduction in their headache frequency, whereas those with exploding migraines generally did not.

**Conclusions:** Our study supports the hypothesis that patients with imploding and ocular migraines are more responsive to BTX than those with exploding migraines. Injections of BTX at doses appropriate for cosmetic purposes may be sufficient to prevent migraine attacks.

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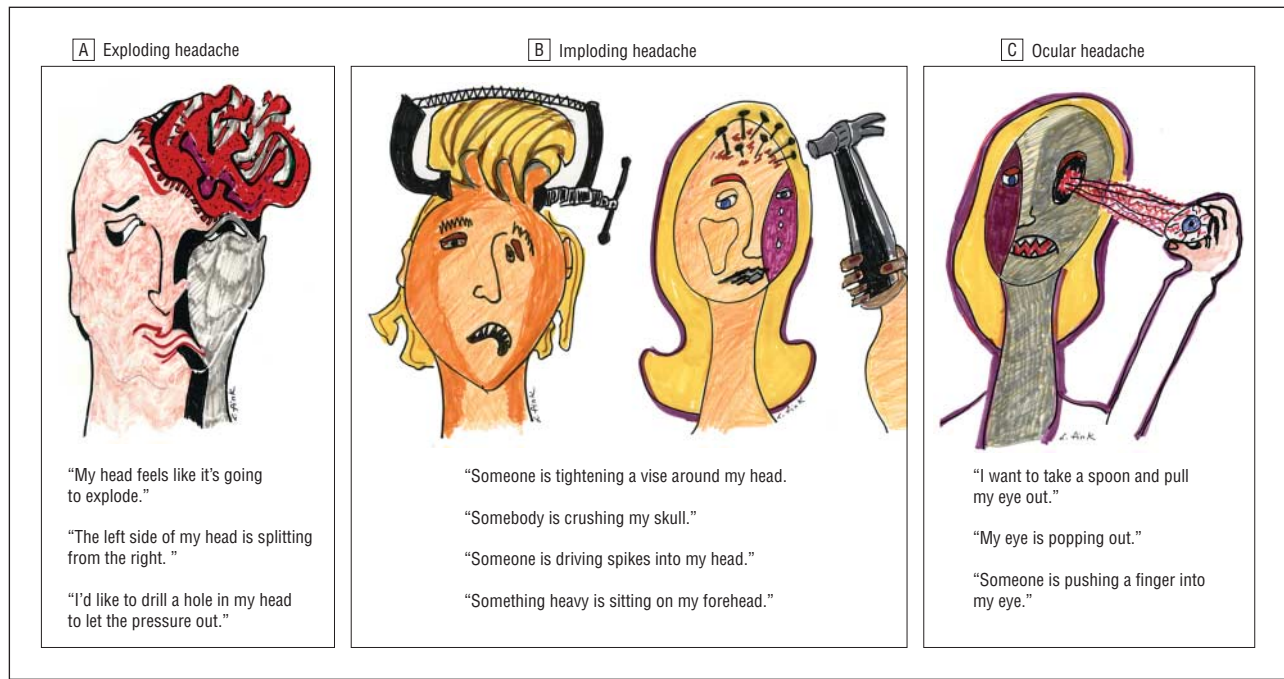
**M**IGRAINE HEADACHES affect approximately 28 million Americans and 2% to 15% of the population worldwide.<sup>1</sup> Migraine is a debilitating neurovascular disorder characterized by severe throbbing, often unilateral headaches that are sometimes associated with nausea, vomiting, photophobia, or phonophobia. Migraine accounts for a significant economic burden on society, being responsible for 112 million bedridden days each year and resulting in \$14 billion in reduced productivity and missed workdays.<sup>2</sup> Therefore, the search for successful therapies for migraine is paramount.

While conducting clinical trials on botulinum toxin type A (BTX) for the treatment of hyperfunctional facial lines, Binder et al<sup>3</sup> recognized a correlation between pericranial BTX injections and the alleviation of migraine headache symptoms. The initial promise of a new prophylactic therapy for migraines was met by the challenge of replication of these results. Subsequent retrospective, open-label medical record reviews and double-blind, placebo-controlled trials have failed to consistently demonstrate superiority of BTX over placebo. Drawing conclusions from

these trials is difficult because of the varying doses of BTX used (ranging from 25 to 300 U), differences in injection sites (fixed injection points, a follow-the-pain technique, or a combination of the 2), use of concurrent prophylactic medications, and varying thresholds that define *response* and *nonresponse*. Despite inconsistent efficacy data, these trials have demonstrated the overall safety and tolerability of BTX for the prevention of migraine and other headache disorders.

Researchers have searched for patient characteristics that may predict a favorable treatment response. In 1 prospective, open-label study<sup>4</sup> of 74 patients from a headache clinic, duration of illness emerged as a predictor of treatment response, whereas frequency of migraine attacks, presence of analgesic overuse, total BTX dose, and presence of underlying muscle tenderness were not predictive.

Jakubowski et al<sup>5</sup> prospectively studied 42 migraine patients to find a neurologic marker that would differentiate between those patients who respond to BTX treatment and those who do not. To their surprise, those who responded and those who did not respond were sharply divided in their descriptions of the directionality of their headache



**Figure.** Migraine headache types. A, Exploding; B, imploding; and C, ocular. Reproduced with permission from the International Association for the Study of Pain from Jakubowski et al.<sup>5</sup>

pain. Of the 39 with clear response, 87% described their pain as crushing and vicelike (imploding) or eye-popping (ocular). Conversely, 92% of the 24 without response described their headache pain as a buildup of pressure inside their head (exploding). To test the validity of this finding, a retrospective study was conducted at 2 other headache clinics, in which patients who were already undergoing prophylactic treatments with BTX were interviewed. Again, the only factor that distinguished those who responded from those who did not respond was the description and directionality of their headaches.

In the study by Jakubowski et al,<sup>5</sup> a total of 100 U of BTX were injected using a fixed-dose technique into the following muscle groups: frontal or glabellar, occipital, temporalis, trapezius, semispinalis, and splenius capitis. The purpose of our study was to determine whether BTX injections at doses typical for upper-face cosmetic purposes, which differ significantly from the doses used in the aforementioned study, could effectively prevent imploding and ocular but not exploding migraine headaches. By recruiting study participants from a pool of existing patients who paid for cosmetic BTX injections, we aimed to eliminate any study bias involving volunteers who may have been influenced by the potential for cosmetic gain from free BTX injections.

## METHODS

The study was performed in an outpatient dermatology group practice setting according to a protocol approved by the Western Institutional Review Board. Study participants were recruited among existing patients who had received or were planning to receive BTX injections for upper-face cosmetic purposes (glabella, forehead, and periorbital areas) but also testified to having a history of migraine headaches. At visit 1, patients were

interviewed by dermatologists (C.C.K., M.M.B., S.A.W.) who had been trained to take a detailed migraine history that documented demographic information, headache characteristics, frequency and duration of migraine attacks before BTX injections, and migraine type. To help patients distinguish among imploding, exploding, and ocular headaches, the dermatologists presented them with a figure from the article by Jakubowski et al<sup>5</sup> (**Figure**).

Patients were treated on visit 1 only if it coincided with their usual scheduled treatment intervals or if it was their first treatment. The physicians who performed the injections were masked to the subtype of migraine the patients had reported. The treatment protocol did not alter previous doses, injection patterns, or treatment intervals recorded in the medical records of the patients. Furthermore, patients were not asked to change the ingestion habits of their usual medications to relieve acute migraine attacks. Patients received intramuscular BTX injections (Botox; Allergan Inc, Irvine, California). Each 100-U vial was diluted with 5 mL of preserved 0.9% saline, which yielded a preparation of 2.0 U per 0.1 mL. Muscles typically treated for upper-face cosmetic rejuvenation included procerus, corrugators, frontalis, and orbicularis oculi. Extra trigger points in the temporalis, occipitalis, cervical paraspinal, and trapezius muscles were injected in a subset of patients who reported muscle tenderness that coincided with their migraine headaches. At visit 2, which took place 3 months after the initial visit, patients returned to the clinic for a structured interview with a headache specialist (R.B.), who knew the patients had received BTX injections but was masked to the effects these injections had on their migraine headaches and whether they were of the imploding, exploding, or ocular subtype. The sole purpose of the structured interview by the headache specialist was to confirm the headache type(s) for each patient. After this visit, patients were contacted to summarize their headache frequency and duration in the second and third months after BTX injections.

The primary outcome measured was the difference in migraine frequency before and after BTX treatment, reported in

**Table 1. Patient Characteristics and Botulinum Toxin Type A Injection Sites and Doses**

Patient No./ Sex/Age, y	Migraine History Duration, y	Injection Sites	Mean Dose Injected to Trigger Points, U	Mean Total Dose Injected per Session, U
1/F/69	54	G/F/P	NA	31
2/F/57	27	G/F/P	2	46
3/F/54	46	G/F/P	20	56
4/F/44	12	G/F/P	NA	26
5/F/40	20	F/P	NA	37
6/F/51	39	G/F	20	40
7/F/56	47	G/F/P	48	78
8/F/47	29	G/F/P	NA	40
9/F/44	31	G/F/P	32	55
10/F/44	23	G/F/P	32	46
11/F/57	27	G/F/P	NA	44
12/F/73	66	G/F	8	21
13/F/26	6	G/F/P	16	58
14/F/40	2	G/F/P	NA	56
15/M/61	2	G/F/P	NA	55
16/F/24	13	G/F/P	NA	40
17/F/80	72	G/F/P	4	52
18/F/49	5	G	NA	16

Abbreviations: F, forehead; G, glabella; NA, not applicable; P, periorbital.

number of days per month. Those who responded were defined as having equal to or more than 50% improvement, whereas those who did not respond had less than 50% improvement. Data were analyzed by an independent statistician using the Wilcoxon signed rank test, Mann-Whitney test, and Fisher exact probability test.

## RESULTS

A total of 25 patients were recruited for the study. Six patients did not complete visit 2 and were lost to follow-up. Of the 4 patients who could be reached, 3 stated that there was no relief from their migraines as a result of the BTX injections. Data collected from visit 1 suggest that 2 of those who did not respond had imploding migraines and 1 had exploding or ocular migraines. The 1 who had responded had imploding migraines and reported a 50% reduction in migraine frequency. Headache subtype could not be definitively assigned because these patients did not undergo the confirmatory visit 2 interview with the headache specialist (R.B.). Therefore, data from these patients could not be included in our analysis.

One patient was excluded from data analysis because her baseline frequency was only 2 to 3 migraine headaches per year; thus, a reduction in migraine frequency would not be detectable under statistical tests. Of the remaining 18 patients (17 women and 1 man), 1 (patient 7) had 2 distinct headache types, which were included in our analysis (patient 7a and 7b). Therefore, 19 total data points were analyzed.

Patient characteristics and BTX injection sites and doses are summarized in **Table 1**. The mean age of the patients was 50.9 years (range, 26-80 years). The average duration of migraine headaches for patients with a history of migraine was 28.9 years (range, 2-72 years). The mean dose of BTX was calculated for the relevant upper-face treatment sessions per patient. The resulting aggregate

mean dose of BTX injected was 45.7 U per treatment session (range, 16-78 U).

The medications reported in the interviews with patients were ones commonly used at the acute onset of migraine headaches. These medications included serotonin agonists (sumatriptan succinate, zolmitriptan, eletriptan hydrobromide, and almotriptan malate), nonsteroidal anti-inflammatory drugs (aspirin and ibuprofen), antiemetics (meclizine hydrochloride), opiates (acetaminophen and hydrocodone bitartrate), and combination analgesics (acetaminophen-butalbital-caffeine, aspirin-butalbital-caffeine, acetaminophen-isometheptene-dichloralphenazone, and aspirin-acetaminophen-caffeine). None of the patients reported taking medications for the purpose of migraine prophylaxis, such as  $\beta$ -adrenergic blockers, calcium channel blockers, tricyclic antidepressants, or anti-convulsants. Patients had been instructed not to change medication use for the duration of the study to exclude this as a possible confounding factor.

Our results confirmed the findings of the study by Jakubowski et al.<sup>5</sup> Among those who responded, 10 patients had imploding or ocular headaches and 3 patients had exploding headaches. Among those who did not respond, 6 patients had exploding headaches; none had imploding or ocular headaches. The Fisher exact probability test showed that this difference was significant ( $P=.003$ ). Migraine frequency for those who responded was reduced from a mean (SD) of 6.8 (1.2) days per month to a mean (SD) of 0.7 (0.2) days per month after BTX injections, whereas the respective reduction in migraine frequency for those who did not respond was from 14.1 (5.1) days per month to 13.7 (5.2) days per month. Although the mean pretreatment migraine frequency was higher for those who did not respond compared with those who responded, this difference was statistically insignificant using the Mann-Whitney test ( $P=.28$ ).

**Table 2. Migraine Subtype and Response to Botulinum Toxin Type A Injections**

Patient No.	Migraine Subtype	Migraine Frequency, d/mo		Improvement, <sup>a</sup> %	R vs NR	Extra Trigger Points Injected
		Before Botulinum Toxin Type A	After Botulinum Toxin Type A			
1	Exploding	3.0	1.0	66	R	No
2	Imploding, ocular	9.0	1.0	87	R	Yes
3	Exploding	10.0	10.0	0	NR	Yes
4	Imploding	1.0	0	100	R	No
5	Exploding, ocular	12.0	1.0	92	R	No
6	Imploding, ocular	12.0	0	100	R	Yes
7a	Imploding	4.0	1.0	75	R	Yes
7b	Exploding	30.0	30.0	0	NR	Yes
8	Ocular	1.5	0.3	80	R	No
9	Imploding	12.0	1.0	94	R	Yes
10	Exploding	6.0	4.0	33	NR	Yes
11	Exploding	3.0	0.5	84	R	No
12	Exploding, ocular	30.0	30.0	0	NR	Yes
13	Imploding, ocular	2.0	0.1	95	R	Yes
14	Ocular	8.0	2.0	75	R	No
15	Exploding	3.3	3.3	0	NR	No
16	Exploding	5.0	5.0	0	NR	No
17	Imploding	9.0	0.2	98	R	Yes
18	Ocular	12.0	0.6	95	R	No

Abbreviations: R, responded; NR, did not respond.

<sup>a</sup>As determined by documentation from physicians in patient medical records.

The patients who had exploding headaches experienced a mean (SD) reduction in migraine frequency of 11.4 (3.7) days per month to 9.4 (4.0) days per month, whereas migraine frequency in patients with imploding and ocular headaches was reduced from 7.1 (1.4) days per month to 0.6 (0.2) days per month. Using the Wilcoxon signed rank test, BTX effects on migraine frequency were significant for those who responded ( $P=.002$ ) and for the patients with imploding ( $P=.005$ ) headaches but not for those who did not respond ( $P=.30$ ) or patients with exploding headaches ( $P=.07$ ).

Baseline frequency of migraines was not a factor in determining the response of individual patients to BTX injections. For example, patient 18 (who responded) experienced a reduction from 12 to 0.6 migraine-days per month, whereas patient 15 (who did not respond) reported migraine-days per month of 3.3 before treatment and 3.3 after treatment. All but 2 of the patients were classified as having episodic migraines because they experienced migraines on fewer than 15 days per month. The 2 patients (patients 7b and 12) who had migraines 30 days per month also had migraines of the exploding subtype, which could explain why they did not respond to BTX injections.

Most patients (14 of 18) received BTX injections in all 3 upper-facial cosmetic sites: glabella, forehead, and periorbital (Table 1). Extra trigger points, or sites of muscle tenderness, were injected in 10 of the 18 patients (56%) (Table 2). Of these patients, 6 responded and 4 did not respond (both of the headache subtypes of patient 7 were included). It does not appear that BTX injection at points of muscle tenderness determines response status, which affirms the results from previous studies.<sup>5</sup>

## COMMENT

Patients with frequent, disabling, or refractory migraine are candidates for prophylactic treatment. Available therapies for the prevention of migraines (ie,  $\beta$ -adrenergic blockers, calcium channel blockers, tricyclic antidepressants, and anticonvulsants) are often associated with adverse effects. Injections of BTX are generally well tolerated, with no significant adverse events. Indeed, they offer an additional cosmetic benefit in the case of our patients.

Botulinum toxin type A produces muscle paralysis by the inhibition of presynaptic vesicular release of acetylcholine at the neuromuscular junction. However, this action does not fully explain how BTX prevents migraine headaches. Extensive research in this area has failed to elucidate an exact mechanism. There is evidence that BTX affects neuronal signaling pathways of both the peripheral and central nervous systems.<sup>6</sup> Alternatively, BTX may block pain through direct inhibition of peripheral nociceptors<sup>7,8</sup> or indirect anti-inflammatory action.<sup>5</sup>

Currently, there is no established, standardized approach to injection of BTX for migraine prophylaxis. Because of safety concerns, we show that lower doses of BTX injections used for upper-facial cosmetic purposes, approximately 50% of the dosage used in the study by Jakubowski et al,<sup>5</sup> may be sufficient to prevent migraine headaches. Injection of extra trigger points does not appear to affect response status and may not be necessary to achieve successful prophylaxis. However, their presence in our study represents a possible confounding factor, and future prospective studies in which patients do not receive trigger-point injections are necessary to test this premise.

A standardized interview minimizes interobserver variability and allows our hypothesis to be tested in everyday clinical practice. Our questionnaire uses both illustrations and descriptive phrases to help our patients self-categorize their migraines as exploding, imploding, or ocular. It can be easily implemented in a dermatologic office setting to determine the likelihood that BTX injections will help alleviate a patient's migraine headaches.

Previous studies may have reported inconsistent BTX efficacy because data from a large pool of all patients with migraine were analyzed together. By stratifying patients with migraine by their subtype of migraine, future studies may be able to detect a true response of migraine headaches to BTX injections. This practice may lead to breakthroughs in understanding the cause and pathophysiology of migraines and the mechanisms by which BTX provides analgesia against not only migraines but also other types of headache.

These preliminary data are intriguing, and our results provide support for the hypothesis that patients with migraine that is characterized by imploding and ocular headaches are more responsive to BTX than those with migraine characterized by exploding headaches. Although open label in design, this proof-of-concept study also suggests that BTX injections at doses appropriate for cosmetic purposes may be sufficient to prevent migraine headaches. Our findings invite consideration of using BTX injections to prevent migraine headaches and may promote the role of the dermatologist in the treatment of patients with migraine. However, well-controlled trials need to be conducted to confirm these findings.

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