Neurotoxins: Expanding Uses of Neuromodulators in Medicine—Headache

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Summary: Over the course of the past 17 years, since the initial discovery of the association between botulinum toxin-A (BT-A) and the reduction of headache symptoms, the use of this neurotoxin has greatly evolved. BT-A has emerged as an alternative to prophylactic pharmacological therapies in the prevention of chronic migraine headaches, with an excellent safety profile and proven efficacy, and is Food and Drug Administration–approved for on-label use since October 2010. The mechanism of BT-A involves its effect at the neuromuscular junction, inhibition of neuropeptide and neurotransmitter release in peripheral sensory neurons, and retrograde axonal transport allowing for its direct effect on inhibiting central sensitization. Through its diagnostic and therapeutic utility, BT-A has proven to be an integral part in the treatment of chronic headache disorders. (*Plast. Reconstr. Surg.* 136: 104S, 2015.)

The majority of primary headaches fall into 3 categories: cluster, tension, and migraine headache. Pharmacologic treatment is the classic therapy for these disorders, both for abortive and preventative purposes. The use of a neuromodulator, however, for the treatment of headache symptoms is a far more recent discovery. The purpose of this article is to review the role of botulinum neurotoxin (BT) in the treatment of headache symptoms.

Binder et al[1] first noticed the positive effect onabotulinum toxin-A (BT-A) had on migraine headache symptoms while he was conducting clinical trials of BT-A for the treatment of facial lines in the 1990s. The role of BT-A in the field of medicine and plastic surgery has since greatly expanded.[2] The first open-label, noncontrolled study was published in 2000 and demonstrated that BT-A is safe and effective for both acute and prophylactic treatment of migraine headaches.[3] Following these findings, a number of exploratory studies were conducted to further assess the efficacy and safety of BT-A in migraine[4–8] and other headache disorders, including chronic daily headache (CDH)[9–12] and tension headaches.[13–16]

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Received for publication March 8, 2015; accepted May 13, 2015.

DOI: 10.1097/PRS.0000000000001732

BTA FOR MIGRAINE

Early Clinical Evidence

There were initial promising studies on BT-A's impact on episodic migraine.[4,5] However, subsequent randomized, controlled studies failed to show significant differences between BT-A and placebo.[6–8] Simultaneously, studies were conducted to evaluate BT-A's effect on patients with CDH,[9–12] a comprehensive term defined as more than 15 headaches a month, regardless of the underlying etiology. Primary analyses revealed no statistically significant differences between BT-A and placebo; however, subsequent subgroup analysis suggested efficacy in migraine patients with a greater baseline headache frequency.[12] This led to the emergence of the term "chronic migraine," which was initially listed in the *International Headache Classification* 2nd edition (ICHD-2) as a complication of migraine in 2004. In 2006, the revised ICHD-2R defined it as a separate diagnosis.[17] In 2008, Freitag et al[18] examined the efficacy of BT-A in chronic migraine patients without concomitant

Disclosure: *Dr. Guyuron is the majority shareholder at Innovative Medical Equipment and receives royalties from Elsevier for the following textbooks:* Guyuron Rhinoplasty; Plastic Surgery: Indications and Practice; *and* Aesthetic Plastic Surgery Video Atlas. *Dr. Janis is a consultant for LifeCell, received royalties from QMP/CRC Press, and has received one-time honoraria from Bard and Pacira. Mr. Nahabet declares no conflict of interest.*

medication overuse and concluded that it may be an effective form of treatment. The study, however, only evaluated 36 patients.

Promising results from the aforementioned studies were the motivation behind the 2 large, double-blind, randomized, placebo-controlled phase 3 studies conducted to evaluate the efficacy, safety, and tolerability of BT-A in the refined subset of patients with chronic migraine.[19,20] The Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) 1 and 2 trials evaluated the use of BT-A in patients with an average of 20 headache days per month and had previously been inadequately treated by medical therapies either due to their ineffectiveness or due to intolerability. The pooled analysis of the PREEMPT 1 and PREEMPT 2 studies, consisting of 1384 patients, demonstrated a statistically significant decrease in frequency of headache days in the BT-A group compared with placebo group (–8.4 vs –6.6; $P < 0.001$).[21] BT-A was also significantly more effective than placebo in secondary endpoints, including mean change from baseline in frequency of migraine days, number of moderate-to-severe headache days, cumulative hours of headache, headache episodes, migraine episodes, and proportion of patients with severe Headache Impact Test-6 scores. Importantly, patients administered BT-A also had significant improvement in their health-related quality of life measures, indicating clinically meaningful benefits to the patient.[21] Shortly after the PREEMPT trials, in October 2010, the US Food and Drug Administration approved BT-A injection for the prevention of headaches in adult patients with chronic migraine.[22]

Epidemiology and Current Standard of Treatment

Chronic migraine affects approximately 1.4–2.2% of adults in the general population.[23,24] The most recent ICHD (3rd edition, beta) defines chronic migraine as headache occurring on ≥15 days per month for more than 3 months, with features of migraine headache on ≥8 days a month.[25] Population studies estimate that of patients with episodic migraine, 2.5% a year will transition to chronic migraine.[26] Population-based surveys estimate that only 6–13% of patients with migraine who could benefit from preventive treatment are currently receiving therapy.[27–29] In addition, studies have revealed that approximately 35% of patients are noncompliant with their prophylactic medications[30] and 75% discontinue treatment after 1 year,[31] due to either adverse events or difficulty with daily administration. The remarkable safety profile and the duration of action of BT-A remove the issue of compliance and make it an appealing alternative to prophylactic medications. Studies directly comparing BT-A with amitriptyline, topiramate, and valproic acid have revealed comparable efficacies.[32–34] However, as described by Jackson et al[35] in a meta-analysis, none of these studies were designed as equivalence studies, and they were all underpowered to show significant differences. In addition, most of these studies lost several patients to follow-up.

Injection Protocol

Studies have described various methods of injection of BT-A. The fixed-site approach utilizes fixed symmetrical injections in predetermined sites, within a range of predetermined doses. Initial studies employed this type of paradigm to determine which muscles and doses were effective.[36,37] An alternative paradigm was the "follow-the-pain" approach, whereby sites and doses were adjusted depending on the patient's constellation of symptoms and the location of pain and tenderness, both reported and elicited.

An early randomized placebo-controlled trial determining the effect of BT-A on CDH gave insight into the appropriate dose of injections.[10] Silberstein et al[10] tested the effects of 225, 150, and 75 U of BT-A on CDH. The 225-U and 150-U treatment groups observed greater decreases in headache frequency comparison with the 75-U group; however, the 225-U group experienced a greater number of adverse events. Therefore, it was determined that the optimal dose for maximum efficacy and tolerability was 150–200 U.

The PREEMPT clinical trials utilized 155 U to 31 injection sites across 7 head and neck muscles using the fixed-site injection paradigm (Fig. 1) and additional injections of up to 40 U to 8 additional injection sites across 3 head and neck muscles using the follow-the-pain paradigm (Fig. 2), thereby confirming the dosing range and verifying the efficacy of this combined paradigm.[19,20,36] The PREEMPT technique is considered the standardized technique of injection, with a maximum dose of 195 U across 39 sites every 12 weeks. Although the injection sites are named after muscles, they are meant to target trigeminal nerve branches, particularly the supraorbital, supratrochlear, and auriculotemporal nerves, the greater, lesser, and third occipital nerves, and the cervical sensory rami from C3 to C5 and located in the neck and shoulder regions (Table 1).[36,37]

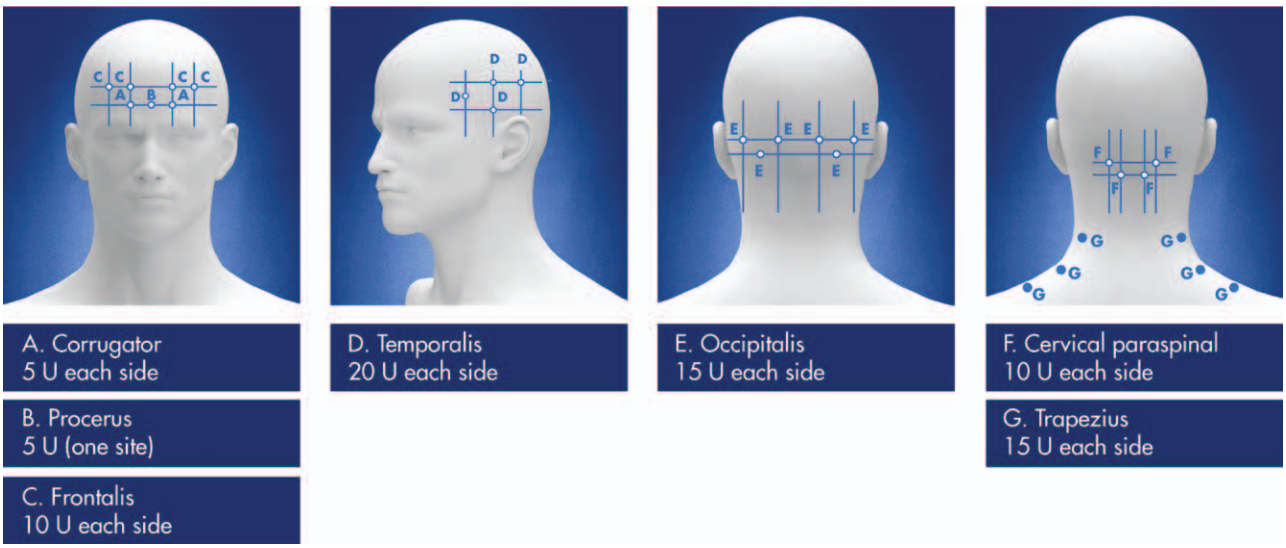

Fig. 1. Fixed-site, fixed-dose injection site locations: the (A) corrugators, (B) procerus, (C) frontalis, (D) temporalis, (E) occipitalis, (F) cervical paraspinal, and (G) trapezius muscle injection sites.

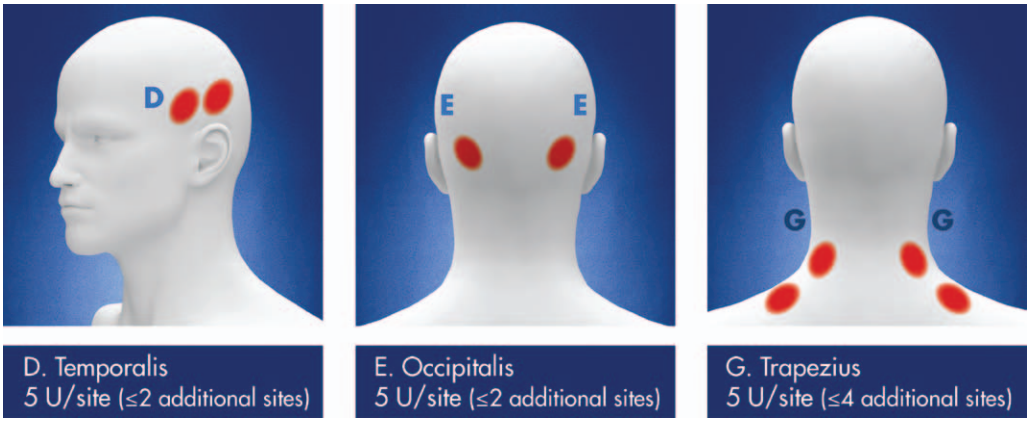

Fig. 2. Follow-the-pain muscle areas: optional injections are distributed between the right and left (D) temporalis, (E) occipitalis, and (G) trapezius muscles in areas of maximal tenderness and/or pain.

Table 1. Injection Site Nomenclature and Respective Nerves

Injection Site	Targeted Sensory Nerves
Procerus, corrugator, and frontalis	Supraorbital and supratrochlear
Temporalis	Auriculotemporal and zygomaticotemporal nerves
Paraspinal and occipitalis	Greater and third occipital nerves
Trapezius	Lesser occipital nerve and C3–C5 cervical sensory rami

Most neurologists utilize the injection paradigm described in the PREEMPT trials, which has been previously described in detail by Ashkenazi and Blumenfeld.[37] The senior author, however, employs a different technique that targets the major migraine headache trigger sites. Twenty-five units are injected in the globular area (12.5 U) of BT-A in 0.5 cc solution on each side through single penetration using a 30-gauge needle for the frontal trigger sites. The injection starts superficially in the subcutaneous region laterally at about 1.5 cm above the inner quarter of the eyebrow and deeper as you get closer to the midline to minimize the potential for lid ptosis. For the temporal site, 25 U of BT-A, dissolved in 0.5 cc, is injected into the deep temporal fascia in a fan shape using the entire length of the 30-gauge needle. The occipital area is treated with 25 U of BT-A for each side in 0.5 cc of saline injected deep in the occipital area using the entire length of the needle. BT-A is injected diffusely in lesser amounts, focusing mostly in an area 3 cm from the occipital tuberosity and 1.5 cm from the midline.

Although some studies have evaluated the cumulative benefit and adverse events related to multiple injection cycles, further studies are required to evaluate the long-term effects of BT-A.[38]

Positive Predictors

Jakubowski et al[39] conducted a study to better understand predictors of a positive response from BT-A and found that 94% of patients with imploding type headache ($n = 31$) and 100% of patients with ocular headache ($n = 5$) responded to injection. Mathew et al[11] reported that patients with unilateral headache, scalp allodynia, and pericranial muscle tenderness also tended to respond more favorably to injection. This information is helpful in guiding patient selection and paving the way for future studies to shed more light on the therapeutic utility of BT-A.

Mechanism of Action

BT is produced by the anaerobic bacteria *Clostridium botulinum*.[40] Seven antigenically distinct BT serotypes have been identified (A-G); however, only serotypes A and B are used in medical treatment.[37] Multiple formulations of BT serotype A exist, including onabotulinumtoxinA (Botox; Allergan Inc., Irvine, CA), abobotulinumtoxinA (Dysport; Ipsen Ltd., Wrexham, United Kingdom), and incobotulinumtoxinA (Xeomin; Merz Pharmaceuticals, Frankfurt am Main, Germany). Studies evaluating the use of Dysport in patients with episodic migraine have revealed no statistically significant differences in comparison with placebo.[41,42] Although it is possible that Dysport and Xeominn may be effective in patients with chronic migraine, large randomized controlled studies proving tolerability and efficacy would be required to justify their use. Currently, these formulations are not indicated. OnabotulinumtoxinA remains the most widely used and investigated formulation.

BT-A likely has multiple mechanisms of action, yet the best understood is at the level of the neuromuscular junction. The impaired release of acetylcholine causes a graded chemical denervation, resulting in temporary muscle paralysis. Muscle activity is regained over the course of 2–6 months via terminal axonal sprouting.[37,43,44]

In addition to muscle paralysis, pain reduction has also been observed with the use of BT-A. Although BT-A's role in pain reduction has been long observed, the mechanism has only been recently elucidated. As early as 1987, it was reported that in patients with focal dystonia and hemifacial spasms, pain relief had been achieved in areas where there was no reduced muscle activity.[45] More recently, the analgesic effect of BT-A has been described, independent of its effect on muscle, and verified in clinical studies of chronic neuropathic pain and diabetic neuropathy patients.[46,47]

Several recent studies describe the mechanism by which BT-A exerts its analgesic effect.[43,48–50] Internalization of the toxin occurs not only in motor nerves but also in sensory nerves, where it is thought to play a role in the inhibition of pain-related neurotransmitters, such as glutamate, substance P, and calcitonin gene–related peptide. This neuromodulatory effect of BT-A inhibits peripheral nerve sensitization, which is the process of progressive sensory neuronal hyperactivity and decreased pain threshold in patients with migraine due to the repeated release of these proinflammatory mediators.[51,52] Inhibition of peripheral sensitization also indirectly results in reduced central nervous system excitability, also known as central sensitization.

Muscular contraction is also thought to release proinflammatory mediators calcitonin gene–related peptide and glutamate, which can activate and sensitize surrounding sensory neurons. Therefore, muscle relaxation can also play a role in decreased peripheral sensitization.[49,50]

More recently, it has been hypothesized that there is retrograde transport and transcytosis of BT-A along afferents to reach second-order nociceptive neurons and the central nervous system.[52,53] Several neurophysiological studies have supported this theory of retrograde transport and therefore the central effect of BT-A.[54,55]

BT-A as a Positive Predictor of Migraine Surgery

Guyuron et al[56] first noticed the association of improvement or elimination of migraine headache in patients who underwent cosmetic browlifts in 2000. Over the past 15 years, migraine surgery has emerged as an extremely efficacious and safe treatment for migraine headaches. Multiple clinical studies have verified the efficacy and safety of migraine surgery, which has resulted in significant improvement or complete elimination of migraine headache in nearly 90% of patients.[57–63] The procedure targets migraine headache trigger sites defined as peripheral sensory nerves that are irritated by surrounding muscle, fascial bands, vessels, and/or bone. Rhinogenic trigger sites include

the septum, turbinates, and concha bullosa. Early on, a diagnostic algorithm was developed that utilized BT-A to identify trigger sites.[59] The diagnostic injection technique is identical to the treatment technique used by the senior author with the exception that each site is injected 1 month apart. More recently, due to the discovery that not all irritation points are muscular, a newer algorithm has been established.[64] The detection of migraine headache trigger sites currently employs other diagnostic modalities in addition to BT-A injection, such as nerve blocks, computerized tomography scans, and use of a handheld Doppler. Lee et al[65] have determined that a positive response to BT-A is a prognosticator of migraine surgery success. Therefore, BT-A remains a useful tool in patient selection for migraine surgery and identification of migraine headache trigger sites.

BTA AND OTHER HEADACHE DISORDERS

Tension-Type Headache

Although it was speculated for some time that BT-A may be effective for tension-type headaches, randomized controlled studies have shown no significant improvement between BT-A and placebo in patients with tension-type headache.[13–16,35]

Headache Associated with Cervical Dystonia

Although no studies have established the prevalence or association of headache in cervical dystonia, noncontrolled studies have shown that BT-A in patients with cervical dystonia improves their concurrent headache and migraine symptoms.[66,67]

Headache with Whiplash Injury

A randomized controlled study of 26 patients compared the effects of BT-A administration with those of placebo administration in patients suffering from chronic headache due to cervical whiplash injury, which showed significant improvement in pain and range of motion in comparison with placebo.[68]

Nummular Headache

A case series of 4 patients described BT-A to be well tolerated in patients with persistent nummular headache refractory to other treatments; however, well-designed randomized controlled studies are required to prove clinical benefits in this group of patients.[69]

CONCLUSIONS

Numerous studies have validated the administration of BT-A as a safe and efficacious treatment option for patients with chronic migraine. Although the exact mechanism of this neurotoxin and its effect on the complex pathophysiology of migraine has yet to be completely described, it has proven to be an extremely efficacious diagnostic and treatment modality and a promising alternative to pharmacologic therapies.

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