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Treatment of migraine headache with botulinum toxin type A

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Worldwide prevalence of migraine is estimated to be 13% to 17% in women and 8% to 14% in men based on meta-analyses of international data collected from 1962 to 1992 [1–3]. In the United States, prevalence is estimated at 18% in women, 7% in men, and 13% overall, with higher prevalence among 35- to 45-year-olds, lower income populations, and Caucasians [4]. The sex ratio is equal before puberty, then increases in favor of women until 40 to 45 years of age [5–7]. Overall, migraine is twice as prevalent in women than in men. Among female migraineurs, 60% experience at least one severe attack per month; 42% of this subgroup experience at least four severe attacks per month [8].

The effect of migraine on quality of life is profound. Nearly all migraine patients experience functional impairment because of their condition; more than half report severe impairment or required bed rest [4]. It is estimated that migraine results in 112 million bedridden days in the United States per year and results in an annual cost to employers of $13 billion [9]. Given the prevalence pattern by age, most of these days occur during the most productive employment and most important child-rearing years [10]. The effect of migraine extends beyond the attacks themselves in terms of quality of life, productivity, and comorbidities, such as depression, anxiety disorders, epilepsy, and stroke [8]. Most migraineurs do not seek medical treatment, instead relying on over-the-counter medications [4], because they believe that effective prescribed treatments do not exist [10].

Originally, migraine was classified as either classic or common. In 1988, the International Headache Society (IHS) published guidelines for discriminating among 13 major types of headache [11] because of the inconsistency of headache definitions and the resulting difficulty in epidemiologic and pathophysiologic study; as a result of this classification, classic migraine became "migraine with aura" and common migraine became "migraine without aura." Migraine can be episodic or chronic, but has unique combinations of neurologic, gastrointestinal, and autonomic symptoms that differentiate it from other headache conditions.

Acute medication for migraine typically consists of simple analgesics for mild to moderate attacks. For moderate to severe attacks, ergot derivatives were originally prescribed as the primary specific treatment but have largely been replaced by triptans, which have displayed a greater receptor specificity and have shown greater effectiveness for the more severe attacks. Opioids are reserved for rescue therapy when other medications cannot be used. Unfortunately, acute medications for short-term symptom relief have limited efficacy and may result in adverse side effects; further, they do not offer prophylactic benefits and have diminished effectiveness if taken over long periods of time. Long-term

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prevention, therefore, is the preferred treatment approach to migraine.

The primary goal of migraine preventive therapy is improved quality of life through decreased frequency and intensity of headache, improved function and decreased disability, and reduced use of medications with improved efficacy of acute therapy. A carefully managed preventive program often begins with patient education so that future attacks can be minimized or avoided. Although some of the proposed etiologic factors for migraine are out of the patient's control, such as heredity [12] and cyclical hormone changes in females [13], others are amenable to lifestyle changes. Examples of such factors are stress, smoking, caffeine and alcohol consumption, lack of exercise, sleep pattern, quality, and duration, and, in females, oral contraception and estrogen replacement therapy (see references [5,14–16]). Some medications have also been hypothesized to initiate or increase the frequency of migraine attacks, namely nitroglycerin, certain calcium channel-blockers, tetracycline, and sildenafil citrate [16].

Several drugs are prescribed as prophylactics for migraine, including anticonvulsants, antidepressants, beta blockers, calcium channel antagonists, conventional or selective nonsteroidal anti-inflammatory drugs, and serotonin antagonists. As with all systemic acute medications, there are drawbacks to using these classes of drugs for migraine prevention. Efficacy is inconsistent and tends to decrease over time. Unpleasant side effects can occur with each of these types of drugs. They include drowsiness, fatigue, dizziness, sexual dysfunction, weight gain or loss, constipation, nausea, dry mouth, and insomnia. Drug-to-drug interactions are also a source of concern. None of the above mentioned drugs are approved by the U.S. Food and Drug Administration (FDA) or labeled as such for use in headache treatment or prevention.

The lack of effective pharmacologic therapies for migraine makes the results of recent studies of botulinum toxin A (BTX-A) for migraine particularly compelling. As is frequently the case when new uses are found for existing agents, the effect of BTX-A on migraine was discovered serendipitously. While performing initial clinical trials of BTX-A for hyperfunctional facial lines, the senior author (W.J. Binder) noted a correlation between pericranial injections and migraine symptom relief in 1992. Without a clear-cut mechanism of action to explain the clinical effect, BTX-A as a treatment for migraine was not immediately obvious. Consequently, Binder et al investigated the clinical results which resulted in the first open-label study of BTX-A efficacy on migraine [17].

Summaries of these initial results and other subsequent BTX-A studies in migraine and headache are detailed below.

Clinical trials of BTX-A for migraine

Open-label study, Binder et al, 2000 [17]

Patients who had headache disorders were recruited from private-practice cosmetic surgery, otolaryngology, and neurology clinics who either sought BTX-A treatment for facial wrinkles or other dystonias or who were candidates for BTX-A treatment specifically for headaches. Study subjects were classified as true migraine (n = 79), possible migraine (n = 18) or nonmigraine (n = 9) based on their baseline headache characteristics and IHS criteria. BTX-A injections were administered to the glabellar, temporal, frontal, and, in two subjects, the suboccipital regions of the head and neck. The injection protocol followed predetermined standards for the treatment of hyperfunctional facial lines and facial dystonias [18], although those subjects who were treated specifically for more chronic and intractable headache toward the latter part of the study tended to receive larger doses. Follow-up ranged from 3 to 24 weeks.

Among 77 true migraineurs who were treated prophylactically, 51% (95% confidence interval [CI] = 39% to 62%) experienced complete response (elimination of headache symptoms) with mean (sd) duration of benefit of 4.1 (2.6) months. Complete response was related to lower baseline migraine frequency ($P = 0.06$; Fig. 1) and severity ($P = 0.07$) but "improvement" (at least 50% reduction in frequency or severity of headaches) was not. Although there was no evidence of dose-response (after adjustment for baseline frequency), injection site was a significant predictor of complete response ($P = 0.01$), with 87% of complete responders had received glabellar injections (compared with 66% of non- or partial responders). There was a considerable effect on nausea and vomiting, as well as the other associated symptoms of migraine.

Ten of 13 true migraineurs who were treated for acute symptoms were complete responders (70%; 95% CI = 35% to 93%). All responders improved within 1 to 2 hours postinjection.

There were no reported cases of true eyelid ptosis, diplopia, facial nerve or expression problems, keratopathy, or idiosyncratic or allergic reactions attributable to BTX-A treatment. Two subjects reported transient brow ptosis; other adverse effects were

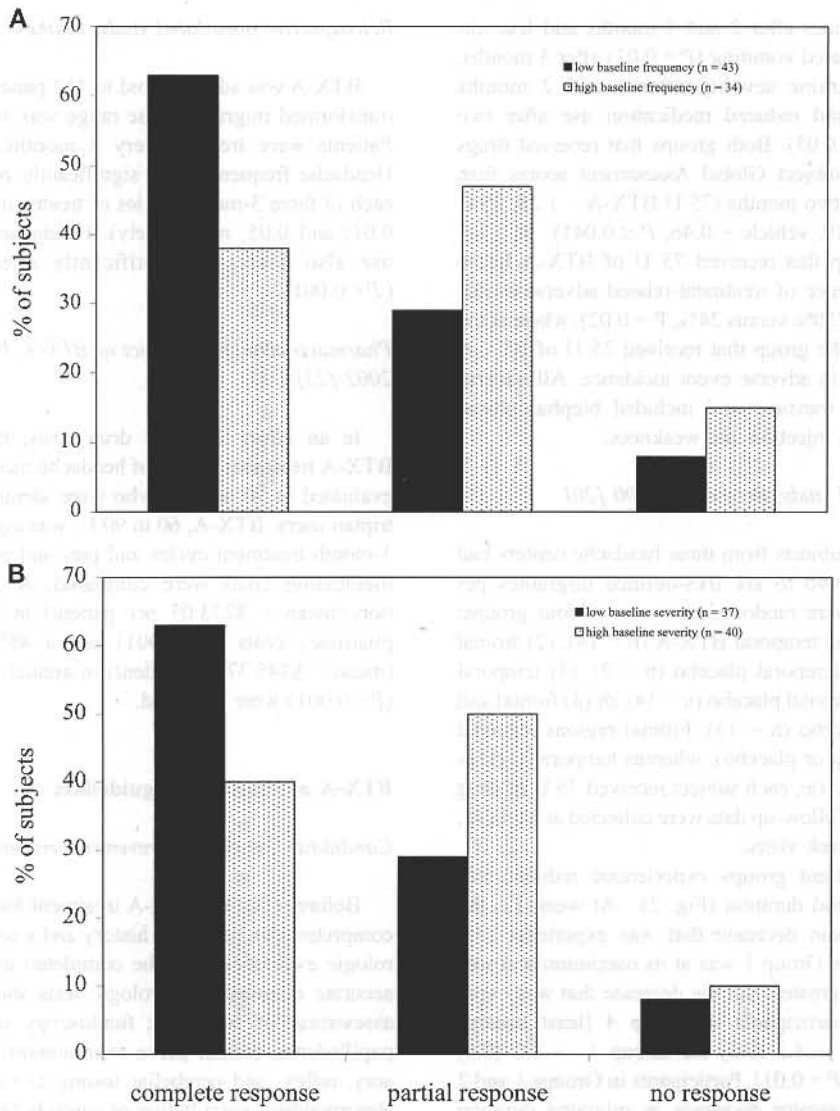

Fig. 1. Response to botulinum toxin type A injections for migraine headache by baseline headache frequency (*A*), and severity (*B*), open label study. *Data from* Binder WJ, Brin MF, Blitzer A, Schoenrock LD, Pagoda JM. Botulinum toxin type A (BOTOX) for treatment of migraine headaches: an open-label study. Otolarygol Head Neck Surg 2000;123(6):669–76.

limited to transient local pain and ecchymosis at the injection site.

Findings from this study became the impetus for the initiation of subsequent placebo-controlled trials.

Double-blind study, Silberstein et al, 2000 [19]

Eligible subjects from 12 headache centers had histories of two to eight moderate to severe IHS-defined migraines per month and were randomized to one of three groups: (1) vehicle (n = 41), (2) BTX-A, 25 U (n = 42), or (3) BTX-A, 75 U (n = 40). Symmetrical injections were administered to the frontal, temporal, and glabellar regions of the head. Follow-up data were collected at 3 monthly postinjection visits.

Compared with vehicle, the group who received 25 U of BTX-A experienced fewer moderate to

severe migraines after 2 and 3 months and less migraine-associated vomiting ($P = 0.01$) after 3 months, reduced migraine severity after 1 and 2 months ($P \leq 0.03$), and reduced medication use after two months ($P = 0.03$). Both groups that received drugs had higher Subject Global Assessment scores than vehicle after two months (75 U BTX-A = 1.25, 25 U BTX-A = 1.19, vehicle = 0.46; $P \leq 0.041$).

The group that received 75 U of BTX-A had a higher incidence of treatment-related adverse events than vehicle (50% versus 24%, P = 0.02), whereas the vehicle and the group that received 25 U of BTX-A were similar in adverse event incidence. All adverse events were transient and included blepharoptosis, diplopia, and injection site weakness.

Double-blind study, Brin et al, 2000 [20]

Eligible subjects from three headache centers had histories of two to six IHS-defined migraines per month and were randomized to one of four groups: (1) frontal and temporal BTX-A (n = 14), (2) frontal BTX-A and temporal placebo (n = 2), (3) temporal BTX-A and frontal placebo (n = 14), or (4) frontal and temporal placebo (n = 13). Frontal regions received 45 U (of drug or placebo), whereas temporal regions received 30 U (ie, each subject received 75 U of drug or placebo). Follow-up data were collected at 2-, 4-, 8-, 12- and 16-week visits.

All treatment groups experienced reduced migraine pain and duration (Fig. 2) . At week 12, the amount of pain decrease that was experienced by participants in Group 1 was at its maximum and was significantly greater than the decrease that was experienced by participants in Group 4 [least squares mean (se) = −4.3 (0.6) for Group 1, −2.0 (0.6) for Group 4; $P = 0.01$]. Participants in Groups 1 and 2 experienced greater decreases in migraine duration than participants in Groups 3 and 4 but these differences were not significant.

Reported adverse effects included blepharoptosis and injection site reaction and edema; all were mild and transient.

Retrospective open-label study, Blumenfeld [21]

BTX-A was administered to 271 headache patients; 76% were refractory to oral medication, 50% overused oral medication, and 32% suffered from depression. Median dose was 63.2 U and mean duration of treatment was 8.6 months. In patients who had migraine, chronic daily, episodic tension, or mixed headache, BTX-A significantly improved headache frequency and intensity.

Retrospective open-label study, Mathew 2002 [22]

BTX-A was administered to 112 patients who had transformed migraine; dose range was 10 to 100 U. Patients were treated every 3 months, if needed. Headache frequency was significantly reduced after each of three 3-month cycles of treatment ($P < 0.001$; 0.01; and 0.05, respectively). Headache medication use also decreased significantly after treatment ($P < 0.001$).

Pharmaco-economic impact of BTX-A, Blumenfeld, 2002 [23]

In an effort to adjust drug costs, the effect of BTX-A treatment on use of headache medication was evaluated in 50 patients who were identified as high triptan users. BTX-A, 60 to 90 U, was injected in two 3-month treatment cycles and pre- and posttreatment medication costs were compared. A 27% reduction (mean = $273.05 per patient) in total annual pharmacy costs ($P < 0.001$) and a 48% reduction (mean = $345.37 per patient) in annual triptan costs ($P < 0.001$) were observed.

BTX-A administration guidelines

Candidates for BTX-A preventive treatment

Before initiating BTX-A treatment for migraine, a comprehensive headache history and a complete neurologic evaluation must be completed to provide an accurate diagnosis. Neurologic tests should include assessment of cognition; fundoscopy to assess for papilledema; cranial nerve examination; motor, sensory, reflex, and cerebellar testing to rule out focal abnormalities; auscultation of carotids for bruits; and palpation of the superficial temporal arteries. Diagnostic imaging such as MRI or CT scans, as well as laboratory testing, should be done to rule out other secondary causes of headache such as tumor, infection, aneurysms, trauma, metabolic disorders, and systemic illness. In addition, patients must be evaluated for contraindications for BTX-A, including neuromuscular disorders, such as myasthenia gravis and Eaton-Lambert syndrome.

After proper diagnosis and after ruling out causes of secondary headaches, patients to consider as potential candidates for BTX-A preventive therapy are those who have primary disabling headaches who usually meet one of the following criteria: frequent migraine (four or more/month); chronic migraine (15 or more headache days/month), chronic tension-type head-

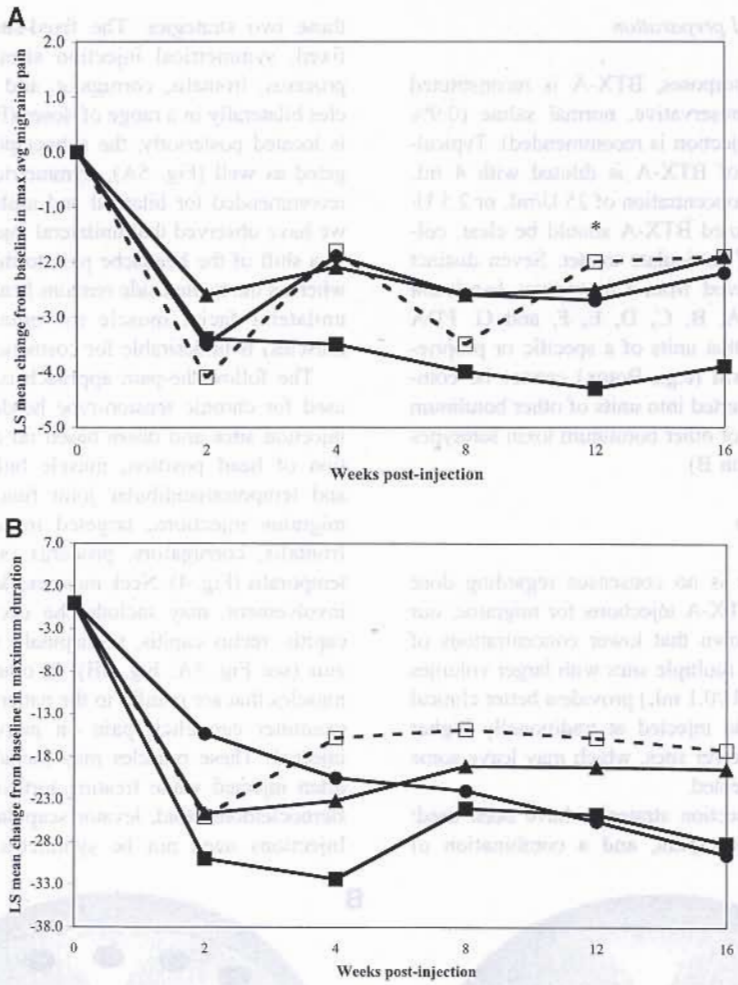

Fig. 2. (*A*) Least squares (LS) mean change from baseline in maximum average pain intensity by treatment group (adjusted for use of rescue medications), region-specific (frontal/temporal) botulinum toxin type A (BTX-A) versus placebo, double-blind study of Brin, 2000 [20]. ■ = BTX-A/BTX-A (n = 14), ●___ = BTX-A/Placebo (n = 12), _____▲ = Placebo/BTX-A (n = 14), □ = Placebo/Placebo (n = 13). Asterisk represents $P = 0.009$ for BTX-A/BTX-A versus Placebo/Placebo at Week 12. (*B*) Least squares mean change from baseline in maximum migraine duration by treatment group (adjusted for baseline and use of rescue medications), region-specific (frontal/temporal) botulinum toxin type A versus placebo, double-blind study of Brin, 2000 [20]. ■= BTX-A/BTX-A (n = 14), ● = BTX-A/Placebo (n = 12), ▲ = Placebo/BTX-A (n = 14), □ = Placebo/Placebo (n = 13).

ache, or "transformed migraine" (*15* or more headache days/month); medication overuse (more than 3 days/week); headache refractory to routine treatment; and contraindications to acute therapy. Other candidates may also have coexisting cranial cervical dystonia, jaw, head, or neck muscle spasm. Patient preference also plays a role in deciding treatment [24].

BTX-A treatment plans should consider patient expectations as well as comorbid conditions. Each patient should be informed of the intended goals of treatment, the purpose of the treatment plan, potential adverse effects, and the need for follow-up care. The goal of preventive headache therapy is to improve the patient's quality of life through measurable decrease in headache frequency and intensity, improved function and decreased disability, reduced use of other systemic medications, and enhanced efficacy of acute headache medications.

Dose, dilution, and preparation

For injection purposes, BTX-A is reconstituted with sterile, nonpreservative, normal saline (0.9% sodium chloride injection is recommended). Typically, a 100 U vial of BTX-A is diluted with 4 mL saline, yielding a concentration of 25 U/mL or 2.5 U/0.1 mL. Reconstituted BTX-A should be clear, colorless, and free of particulate matter. Seven distinct serotypes are derived from *Clostridium botulinum* bacterium: types A, B, C, D, E, F, and G. FDA labeling indicates that units of a specific or proprietary botulinum toxin (e.g., Botox) cannot be compared with or converted into units of other botulinum toxin preparations or other botulinum toxin serotypes (eg, botulinum toxin B).

Injection strategies

Although there is no consensus regarding dose and dilution for BTX-A injections for migraine, our experience has shown that lower concentrations of BTX-A injected at multiple sites with larger volumes of vehicle (eg, 2.5 U/0.1 mL) provide a better clinical outcome than toxin injected at traditionally higher concentrations at fewer sites, which may leave some affected areas untreated.

Three basic injection strategies have been used: fixed-site, follow-the-pain, and a combination of those two strategies. The fixed-site approach uses fixed, symmetrical injection sites that target the procerus, frontalis, corrugator, and temporalis muscles bilaterally in a range of doses (Figs. 3, 4). If pain is located posteriorly, the suboccipital areas are targeted as well (Fig. 5A). Symmetrical injections are recommended for bilateral and unilateral headaches; we have observed that unilateral injections can result in a shift of the headache pain to the uninjected side whereas the treated side remains headache-free. Also, unilateral facial muscle movement (ie, frontalis muscles) is undesirable for cosmetic reasons.

The follow-the-pain approach is most frequently used for chronic tension-type headache and adjusts injection sites and doses based on clinical examination of head position, muscle bulk, tender spots, and temporomandibular joint function. Similar to migraine injections, targeted muscles include the frontalis, corrugators, procerus (see Fig. 3), and temporalis (Fig. 4). Neck muscles, depending on their involvement, may include the occipitalis, splenius capitis, rectus capitis, semispinalis capitis, or trapezius (see Fig. 5A; Fig. 5B). In other circumstances, muscles that are painful to the patient or in which the examiner can elicit pain on palpation should be injected. These muscles may include those that are often injected while treating torticollis, such as the sternocleidomastoid, levator scapulae, and trapezius. Injections need not be symmetrical in dose, but

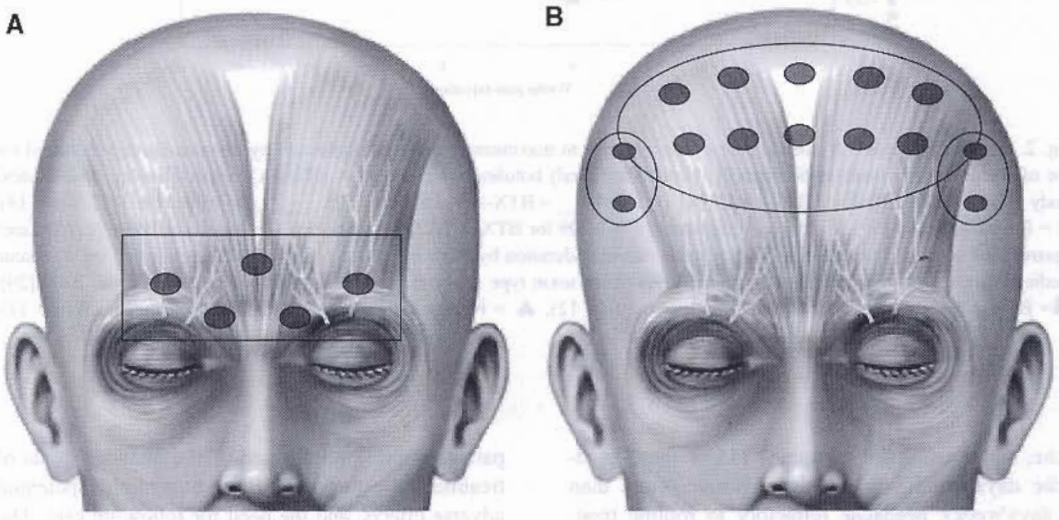

Fig. 3. (*A*) Injection sites within the lower medial forehead or glabella area (Area A) correspond with the corrugator (bilateral) and procerus (midline) muscle groups and with the supratrochlear and supraorbital nerves. (*B*) Areas of injection sites over the forehead, distributed centrally over the frontalis muscle as well as the area of the "temple" or anterior temporal region. Four to eight injection sites per side can usually cover the entire central and lateral forehead areas. Because the frontalis muscle is so close to the skin, the injection of Botox solution over the forehead will immediately diffuse into the frontalis muscle after the needle pierces the skin. The diffusion of the solution that is injected at each site will diffuse over an area that is approximately 2 cm in diameter.

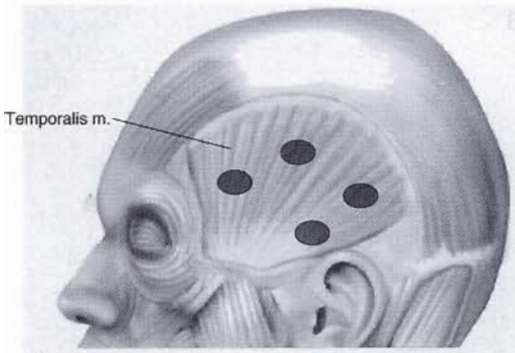

Fig. 4. The four general areas of injection over the region that is occupied by the temporalis muscle. There are normally four to five injection sites with an average dose of 20 U to 25 U per side, averaging approximately 5 U per injection.

should be bilateral to reduce the effects of asymmetrical movement.

The combination approach is most frequently used for patients who have migraine and tension-type headache. Patients are usually classified as those having chronic daily headache, transformed migraine, or chronic daily migraine. Fixed-site injections are supplemented with additional injections in tender or consistently symptomatic areas, which results in a higher overall dose of BTX-A.

The examiner should place a finger on the orbital rim and avoid injections below that point to prevent ptosis. Injection points for the corrugator muscles can be accessed by having patients frown; injection points for the frontalis muscle can be identified by having patients raise their eyebrows. The injection sites into the medial and lateral corrugator muscles correlate directly with the supratrochlear and supraorbital nerves (see Fig. 3A). For injections to the frontalis region, the dose can range from 20 to 40 U dispersed among 8 to 14 injection sites. The frontalis region should be injected symmetrically to avoid facial asymmetry (see Fig. 3B). The area of the forehead over the lateral aspect of the brow should be avoided to prevent brow ptosis (Fig. 6A); however, if injection in this area is required, ptosis can be minimized by injecting the lateral aspect of the infrabrow or eyelid area, specifically targeting the superolateral aspect of the orbicularis oculi muscle (Fig. 6B). If injections are required over the lateral supraorbital region, patients should be informed that brow ptosis may occur. The lateral area of the forehead overlaps with the anterior aspect of the temporal area or "temple." For patients who have pain in this area, an additional 2.5 to 5 U per side may be injected (see Fig. 3B).

It is also important that injections to the temporal area be bilateral to prevent asymmetrical occlusal problems. The most anterior aspect of the temporalis muscle can be identified by having patients clench

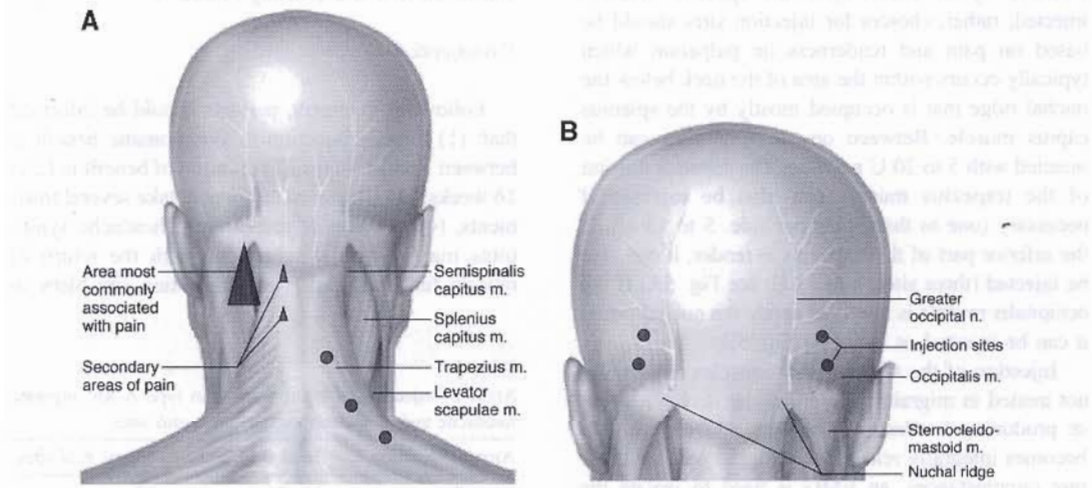

Fig. 5. (*A*) Injection sites for the splenius capitis and trapezius muscles. Usually an area just below the nuchal ridge between the trapezius and sternomastoid muscle is the most common site of pain (*arrow*). This area is occupied primarily by the splenius capitis muscle. Anatomical overlap exists with respect to the upper portion of the trapezius, rectus capitis, semispinalis capitis, and splenius capitis. Therefore, in this region, it is most important that the "area" where the pain is greatest is injected rather than trying to isolate a particular muscle. One to four sites can be injected with 5 U to 20 U per side. (*B*) Injection site for the occipitalis muscle (the area just above the nuchal ridge). Usually one to two injections sites of 5 U to 7.5 U per side is sufficient.

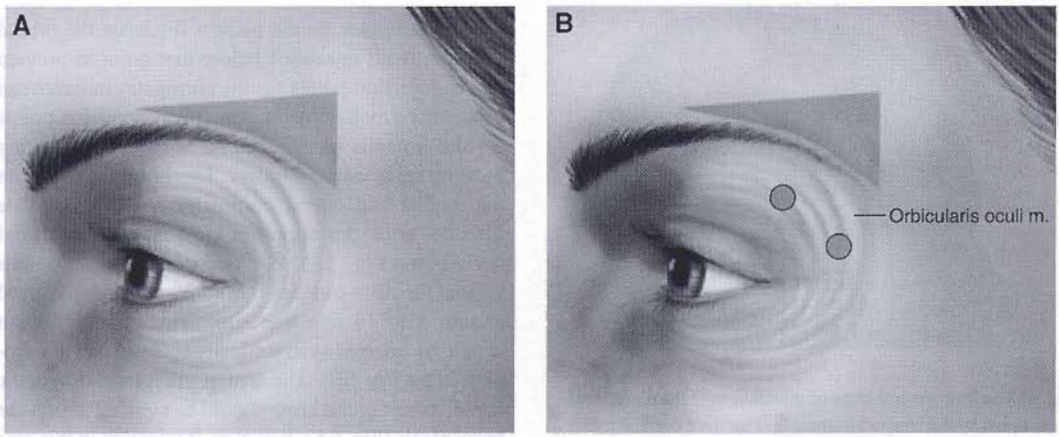

Fig. 6. (*A*) The shaded area above the eyebrow represents an area from the midpupillary line extending laterally to a point approximately 1 cm in vertical height over the lateral most portion of the eyebrow. (*B*) Injecting the superior lateral aspect of the orbicularis oculi muscle with BTX-A (2.5 U to 5 U) weakens the depressor effect of the orbicularis oculi muscle in this area and reduces the amount of brow ptosis if it is necessary to inject the inferolateral portion of the frontalis muscle.

their teeth. Posterior, superior, and inferior aspects can be injected with 0.2 mL per site, resulting in an average dose of 20 U per temporalis muscle (see Fig. 4). Because the temporalis is a large muscle, a larger volume of BTX-A per site can be injected, if necessary, without affecting adjacent muscles.

For patients who have posterior neck pain, the suboccipital, and, less frequently, occipital areas, should be considered for BTX-A injections. It is unnecessary to differentiate the specific muscles injected; rather, choices for injection sites should be based on pain and tenderness on palpation which typically occurs within the area of the neck below the nuchal ridge that is occupied mostly by the splenius capitis muscle. Between one to four sites can be injected with 5 to 20 U per side. The superior portion of the trapezius muscle can also be injected if necessary (one to three sites per side, 5 to 15 U). If the inferior part of the trapezius is tender, it can also be injected (three sites, 5 to 15 U; see Fig. 5A) If the occipitalis muscle is involved above the nuchal ridge, it can be injected as well (see Fig. 5B).

Injection of the anterior neck muscles are usually not treated in migraine.These muscles do have a role in producing headache symptoms when neck pain becomes integrally related to headache pain. In these rare circumstances, an EMG is used to isolate the affected spastic muscle that is contributing to the pain and causing varying degrees of torticollis.

Patients can be in either the sitting or supine position for injections to the frontal and temporal regions but should be in the sitting position for injections to the posterior neck and trapezius areas. Most injections are made with a 0.5-inch 30-gauge needle and a 1-mL syringe directed either perpendicularly or tangentially through the skin to the target site. A 1-inch 30-gauge needle is used to inject the lower part of the trapezius and the other neck muscles. Pain is minimized by avoiding injection of material at the periosteal or intradermal layer. Regionally, vessels should be palpated to avoid intra-arterial injections and superficial blood vessels should be visualized to avoid bruising (Table 1).

Postinjection

Following treatment, patients should be informed that: (1) time of injection to symptomatic benefit is between 3 and 14 days, (2) duration of benefit is 12 to 16 weeks, (3) maximum effect may take several treatments, (4) duration of reduction in headache symptoms may not be synchronous with the return of muscle function, and (5) postinjection site blebs in

Table 1
Areas of injection of botulinum toxin type A for migraine headache and common range of units and sites

Area of injection	Total # of units	Total # of sites
Glabellar	15–25	5
Temporal	15–25	4
Frontal	15–25	multiple (6–10)
Suboccipital (unilaterally)	25	3
Trapezius	15–25	3
TOTAL	85–125	

the forehead region will disappear within a few hours and will reduce the hyperfunctional lines of the face in 3 to 5 days. Patients should be instructed on keeping headache diaries, which document the frequency and location of headache, headache severity, and the amount of headache medication taken over a 4-month period. The Migraine Disability Assessment (MIDAS) can also be used as a measure of treatment success (Appendix A) [25,26]. Objective measurements of treatment effectiveness are important so that clinical response can be evaluated and future treatment sessions can be modified if necessary.

Safety

Reported adverse events that are associated with BTX-A treatment for migraine are rare and mild and include headache, rash, itching, flu-like symptoms, dry mouth, and hoarseness. No systemic reactions have been noted. Temporary ptosis may occur if the area directly over the lateral aspect of the eyebrow requires injection, although this can be minimized if the lateral aspect of the orbicularis oculi muscle in the lateral infrabrow area is also injected (see Fig. 6B). With proper injection technique, eyelid ptosis rarely occurs. As similarly reported in the treatment of patients who have torticollis, weakness of neck muscles is a direct result of dose.

Mechanism of action

In muscle spasm disorders, BTX-A inhibits the release of acetylcholine (Ach) at the neuromuscular junction. If cranial muscle contraction is involved in migraine etiology, this action would be expected to prophylax migraine.BTX-A also seems to relieve other migraine-associated symptoms (eg, nausea and vomiting, visual disturbances, photophobia, and phonophobia), however [17]. Therefore, it seems likely that the mechanism of BTX-A is more complex and is independent of its Ach blocking effect. This is supported by the observation that BTX-A treatment of torticollis provides pain relief in excess of the reduction of inappropriate muscle contraction, which suggests a different pathophysiologic pathway than that related to muscle dysfunction [27,28].

Although the precise mechanism by which BTX-A exerts its clinical response remains unclear, recent reports indicate that it may work through several overlapping mechanisms. Experimental evidence suggests that botulinum toxin, by way of injection or diffusion, affects important sites of action (possibly at the cellular level) other than the currently known neuroeffector sites [29,30]. There is also evidence that botulinum toxin has a direct effect on afferent fibers, suggesting that it may block the sensory system as well as affect the Ia afferent muscle spindle cells [31,32]. In addition, it was noted that botulinum toxins inhibit neurotransmitters and neuropeptides other than Ach, such as calcitonin-gene related peptide, Substance P and glutamate [33–39]. Finally, BTX-A may also act through the nociceptive pain pathway by blocking the C and A delta fibers (group III and IV) mechano- and chemonociceptors [40].

The anatomical correlation in treating wrinkles and migraine is partially explained by the trigemino-neurovascular theory of migraine [41,42]. Anatomic correlation also relates to the fact that BTX-A injection sites frontally correspond to the same areas of the nerves that compose the sensory component of the upper division of the trigeminal nerve. These nerves are the supratrochlear and supraorbital nerves. In a recent experimental study, Aoki [40] showed that in a phase II rat formalin model, BTX-A significantly inhibited secondary inflammatory pain response. It is believed that by inhibiting the release of glutamate from C fibers, BTX-A may interfere with pathways that are associated with central sensititzation [40].

Although the exact mechanism by which BTX-A relieves migraine pain is not yet understood, these observations provide a potential link between the actions of BTX-A at cholinergic nerve terminals and its apparent antivasodilatory and anti-inflammatory effects. Following injection of BTX-A into muscles of the temple or forehead, it seems plausible that cholinergic (parasympathetic) neurons that innervate the extracranial vasculature are recognized, which cause a disruptive effect on the vesicular release of Ach and Ach-like neuropeptides. Because of the known cholinergic effect of BTX-A and the possible colocalization of vasodilatory neuropeptides, inhibition of neurogenic inflammation that results from the neuropeptide release may also prove to be important in migraine relief.

Summary

Migraine is a common headache disorder with profound implications on patients' quality of life and the overall health care system. Traditional treatment options have been less than optimal and many migraine patients lack confidence in over-the-counter and prescribed medications. BTX-A has shown promise as an efficacious, well-tolerated, long-lasting preventive therapy. Completed placebo-controlled trials showed that BTX-A injections for migraine resulted in fewer

headaches, reduced headache severity and duration, reduced migraine-associated symptoms, and reduced use of migraine medications. Because the administration of BTX-A is nonsystemic, reported adverse events have been rare and mild. Larger trials are currently underway to further evaluate BTX-A efficacy and to determine optimal dosing and injection sites.

Based on the collective experience of clinicians in neurology, facial plastic surgery, and otolaryngology, as well as supporting evidence from completed and ongoing clinical trials and theorized mechanism of action, an effective BTX-A approach for treatment of migraine is emerging. With further refinement to its use as prophylactic therapy, BTX-A can potentially be a primary option for candidate migraine sufferers and prescribing clinicians.

Acknowledgments

The authors wish to thank Dr. Janice Pogoda for her assistance in preparing this manuscript.

Appendix A

The Migraine Disability Assessment (MIDAS) Questionnaire

Instructions to Patients: Please answer the following questions about ALL of your headaches over the past 3 months. Write your answer on the line next to each question. Write "0" if you did not do the activity in the past 3 months.

1. On how many days in the past 3 months did you miss work or school because of your headaches? _____ days

2. On how many days in the past 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 when you missed work or school.) _____ days

3. On how many days in the past 3 months did you not do household work because of your headaches? _____ days

4. On how many days in the past 3 months was your productivity in household work reduced by half or more because of your headaches? (Do not include days you counted in question 3 when you did not do household work.) _____ days

5. On how many days in the past 3 months did you miss family, social, or leisure activities because of your headaches? _____ days

MIDAS score Total days _____

What your physician will need to know about your headache:

A. On how many days in the past 3 months did you have a headache? (If a headache lasted more than 1 day, count each day.) _____ days

B. On a scale of 0 to10, on average, how painful were these headaches? (Where 0 = no pain at all; 10 = pain as bad as it can be.) _____

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