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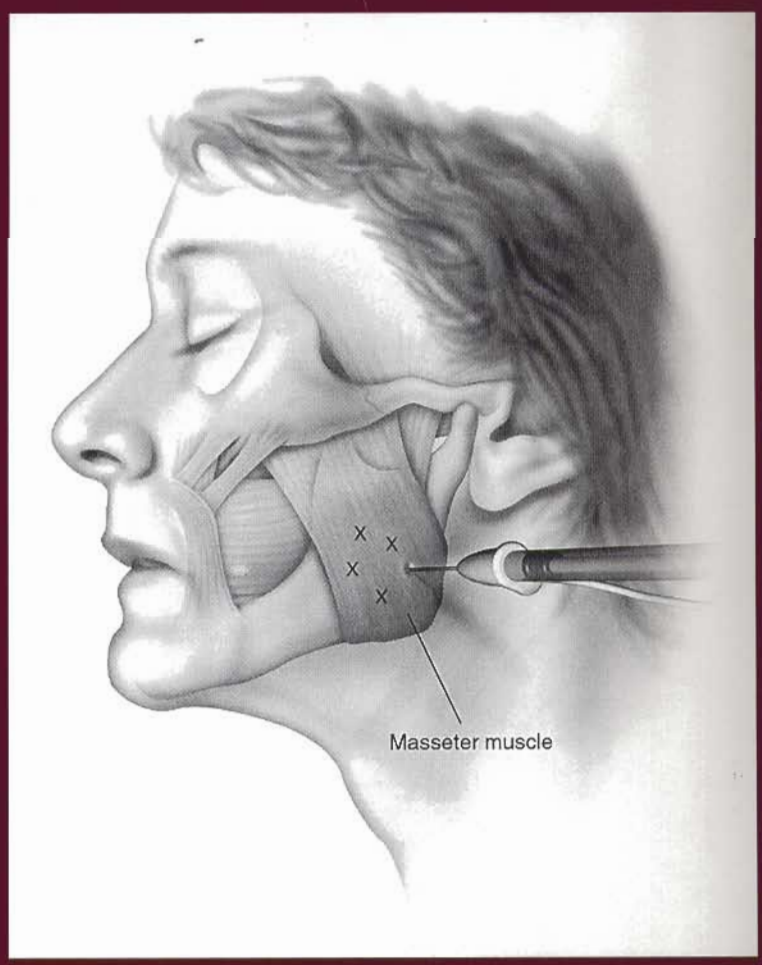

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THE EMERGING ROLE OF BOTULINUM TOXIN TYPE A IN HEADACHE PREVENTION

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Migraine is a common neurovascular disorder characterized by recurrent episodes of head pain that is frequently severe, throbbing, aggravated by movement, and localized to one side of the head. Associated symptoms include nausea, vomiting, and sensitivity to light and sound.[1] Lifetime prevalence of the disorder in the United States may be as high as 18%,[2] with ~28 million Americans presently affected.[3] A preponderance of affected individuals are in their most productive years (aged 25-55 years); therefore, the social and economic burden of disease is considerable. For example, the cost to U.S. employers as a result of missed workdays and reduced productivity is estimated at about $13 billion a year.[4]

Patients whose migraines occur no more than once or twice a month may respond well to acute treatment with nonspecific analgesics such as nonsteriodal anti-inflammatory drugs. Treatment with migraine-specific agents, such as triptans, is indicated for patients with moderate to severe infrequent migraines, or milder headaches that do not respond to nonspecific treatment.[5]

Many patients, however, have an inadequate response to acute therapies or tolerate them poorly. In addition, a significant number of patients suffer frequent headaches; up to 10% of migraineurs have more than 4 attacks per month.[2] Acute medication overuse can itself result in increased frequency of headache, sometimes called "rebound" or "medication overuse" headache, and altered headache characteristics.[6,7] Preventive therapy should be considered for patients with frequent, disabling, or refractory migraine, despite the use of acute treatment, or for those in whom acute therapies are contraindicated or poorly tolerated.[5]

Several categories of preventive treatment exist, with diverse mechanisms of action. The most frequently used agents include β-adrenergic receptor antagonists, such as propanolol and timolol; calcium-channel antagonists such as verapamil; tricyclic antidepressants such as amitriptyline; and anticonvulsants such as divalproex sodium, gabapentin, and topiramate.[2,5,8] In addition, the possibilities of a novel preventive headache treatment, botulinum toxin type A (BoNT-A), are presently receiving vigorous exploration.

Divalproex sodium has demonstrated effectiveness in several controlled trials, but it has the potential to cause hepatotoxicity and thrombocytopenia. Less serious adverse effects include drowsiness, nausea, weight gain, tremor, and hair loss. Beta-blocking agents have shown efficacy; in one small study, propranolol was as effective as divalproex.[9] The adverse effects of the β-blockers include fatigue, decreased exercise tolerance, depression, and sleep disturbance, and they are contraindicated in patients with diabetes, asthma, or depression.[10] Amitriptyline may be a useful agent in patients with comorbid depression, but its systemic anticholinergic, antihistaminic, and α-adrenergic effects limit its tolerability.[10]

Several recently introduced anticonvulsants are under study for effectiveness in preventing migraine.[8] The most promising of these appears to be topiramate; some recently presented controlled data indicate that this agent may reduce headache frequency and severity. However, adverse effects may limit its usefulness, with cognitive impairment, paresthesias, somnolence and fatigue, and visual symptoms reported.[8]

BoNT-A (Allergan, Irvine, CA) has emerged as an effective therapy for headache that may offer significant advantages over other preventive treatments, especially with respect to safety and tolerability. Local injection of this neurotoxin is currently indicated for treatment of a number of neuromuscular disorders including blepharospasm, strabismus, and cervical dystonia.[11] BoNT-A exerts its effects via uptake by cholinergic neurons at the site of injection, resulting in a temporary chemodenervation and a decrease in neuromuscular transmission. Treatment also relieves the pain that accompanies these states of excessive muscle contraction.[12] However, pain relief often precedes muscle relaxation, and may actually exceed the motor benefit.[12] Thus, the pain relief conferred by BoNT-A is probably caused by actions beyond those on neuromuscular transmission, and may help to explain its effectiveness in headache.

Preclinical evidence of specific antinociceptive and/or anti-inflammatory effects of BoNT-A, perhaps involving multiple pathways, is accumulating. For example, data from primary culture and animal models indicate that BoNT-A inhibits the release of glutamate and neuropeptides such as substance P from nociceptive neurons.[13] Peripheral BoNT-A injection also appears to inhibit c-Fos expression, a marker of rapid neuronal firing in response to stimulation, in dorsal horn neurons.[13,14] The net effect of these properties may be a reduction in peripheral sensitization and a decrease in sensory input into the central nervous system, with an indirect effect on central sensitization.[15]

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TABLE 1. Suggested Injection Protocol by Anatomical Site

Muscle	Botox® Units/Site	Number of Injection Sites
Procerus*	2.5-5.0 U	1
Corrugator*		
Medial	2.5 U	2 (1 per side)
Lateral	2.5 U	2 (1 per side)
Frontalis*	2.5 U	8-12 (4-6 per side)
Temporalis*	2.5-5.0 U	8 (4 per side)
Occipitalis†	2.5-5.0 U	2 (1 per side)
Splenius capitis area†	5.0-10.0 U	2
Masseter†	10.0 U	1-2
Trapezius†	5.0-10.0 U	2-6 (1-3 per side)
Sternocleido-mastoid†	5.0-10.0 U	2
Cervical paraspinal muscles†	2.5 U	1-3 per side)

Adapted from Blumenfeld et al.[27]
*For "Fixed Sites" or "Follow-the-Trigeminal Nerve" protocol; injections should be bilateral.
†For "Follow-the-Pain" protocol; injections may be unilateral or bilateral, depending on symptoms and signs.

These antinociceptive effects of BoNT-A may underlie its reported efficacy in migraine and other types of headache. Migraine is a neurovascular event, in which activation of the trigeminovascular system innervating dural and large cranial vessels is accompanied by the release of vasoactive neuropeptides such as calcitonin gene-related peptide, substance P, and neurokinin A. These inflammatory mediators appear to amplify trigeminal nerve sensitivity and stimulate a cascade of events including bradykinin release and mast cell degranulation, resulting in vasodilation, plasma protein extravasation into the perivascular space around the dural blood vessels, and meningeal inflammation.[2,16] The pain of migraine may be generated, in part, by trigeminovascular afferent inputs that ultimately form synaptic connections with thalamic neurons. Peripheral or central sensitization may contribute to the experience of pain in migraineurs, who often also exhibit hyperalgesia and allodynia.[17]

The mechanism by which BoNT-A prevents migraine pain is not yet fully established or understood. In vitro evidence suggests BoNT-A may prevent or diminish the release of neuropeptides involved in pain perception and inflammation. BoNT-A may reduce trigeminal sensitization by inhibiting the release of substance P and other neuropeptides. A growing number of studies support the use of BoNT-A in the prevention of migraine. Some data also suggest its utility in the treatment of tension-type headache (TTH) symptoms. In addition, BoNT-A has been uniformly found to be an extremely safe therapy for headache.[18]

In the largest published placebo-controlled trial to date of BoNT-A in migraine prevention,[19] 123 episodic migraine patients were randomized to receive a 25 U of BoNT-A, 75 U of BoNT-A, or vehicle injected at multiple fixed symmetrical pericranial sites (frontalis, temporalis, corrugator, and procerus muscles). At 2 and 3 months postinjection, patients receiving 25 U of BoNT-A showed a significant reduction in headache frequency, headache severity, acute medication use, and migraine-associated vomiting relative to placebo, although, curiously, those receiving 75 U failed to separate from placebo. A smaller controlled trial (N = 30) examined the efficacy of 50 U of BoNT-A, injected at 15 fixed pericranial sites, in controlling the symptoms of episodic migraine.[20] The active treatment group showed significant decreases relative to placebo in headache frequency and severity, occurrence of nausea, and acute medication use.

Blumenfeld[21] performed a retrospective, open-label investigation of BoNT-A treatment in a large (N = 271) mixed patient population that included patients with chronic daily headache (headache occurring 15 or more days per month, more than 4 hours a day), episodic TTH, episodic migraine, and mixed (episodic migraine and episodic TTH less than 15 days per month) headache. Patients were injected either at fixed sites and/or using the "follow the pain" approach, in which the location and distribution of pain determine the injection site. After treatment, there was a significant reduction from baseline in both frequency and intensity of headache in all headache types ($P < 0.001$), except in the intensity of episodic TTH ($P = 0.09$). These results suggest the efficacy of BoNT-A across multiple headache types.

Several open-label trials suggest that the benefits of BoNT-A are enhanced when multiple cycles of injections are administered. Mathew et al[18] examined the effects of open-label BoNT-A administration in a population of 112 chronic migraine patients on outcomes such as Migraine Disability Assessment Scale (MIDAS) scores and acute medication use. Mean MIDAS scores decreased dramatically, from 85.8 before BoNT-A treatment to 26.2 ($P < 0.001$) after one set of injections. There was also a significant reduction in the use of acute medications. Additional cycles of injections resulted in further significant improvements in MIDAS scores. Tachyphylaxis did not occur, even among patients who had 5 sets of injections.

These findings are buttressed by the results of Troost,[22] who administered 1 to 4 treatment cycles of BoNT-A to 134 patients with intractable headache of mixed type. Subcutaneous and/or intramuscular injections were given at multiple sites in the forehead, temples, neck, and shoulders, using a "follow-the pain" protocol and flexible dosing. Improvement was reported by 84% of patients overall, and the percentage of patients reporting improvement increased among patients undergoing 2 or more treatment cycles.

Some investigators report findings at odds with the results of these studies, however. For example, Silberstein et al[19] failed to show improvement on most measures in the patient group receiving 75 U of BoNT-A. Schmitt et al,[23] in a controlled study of 60 patients with chronic TTH, failed to demonstrate the efficacy of 20 U of BoNT-A injected into fixed temporal and frontal sites with respect to outcome variables such as pain intensity, number of pain-free days, and acute medication use. Rollnik et al[24] also failed to find significant treatment effects of 200 U of BoNT-A injected at fixed pericranial sites in a controlled study of 21 patients with chronic or episodic TTH.

Despite the accumulating evidence supporting the efficacy of BoNT-A in the prevention of migraine, TTH, and

TABLE 2. Summary of Injection Protocols and Clinical Indications

Injection Sites	Clinical Features on History or Exam
Follow-the-trigeminal-nerve (fixed sites)	Migraine or migrainous headache
Follow-the-pain	Tension-type headache
Follow-the-muscles-of-mastication	Temporomandibular disease (TMD)
Follow-the-dystonia	Cervical dystonia (CD)

Adapted from Blumenfeld et al.[27]

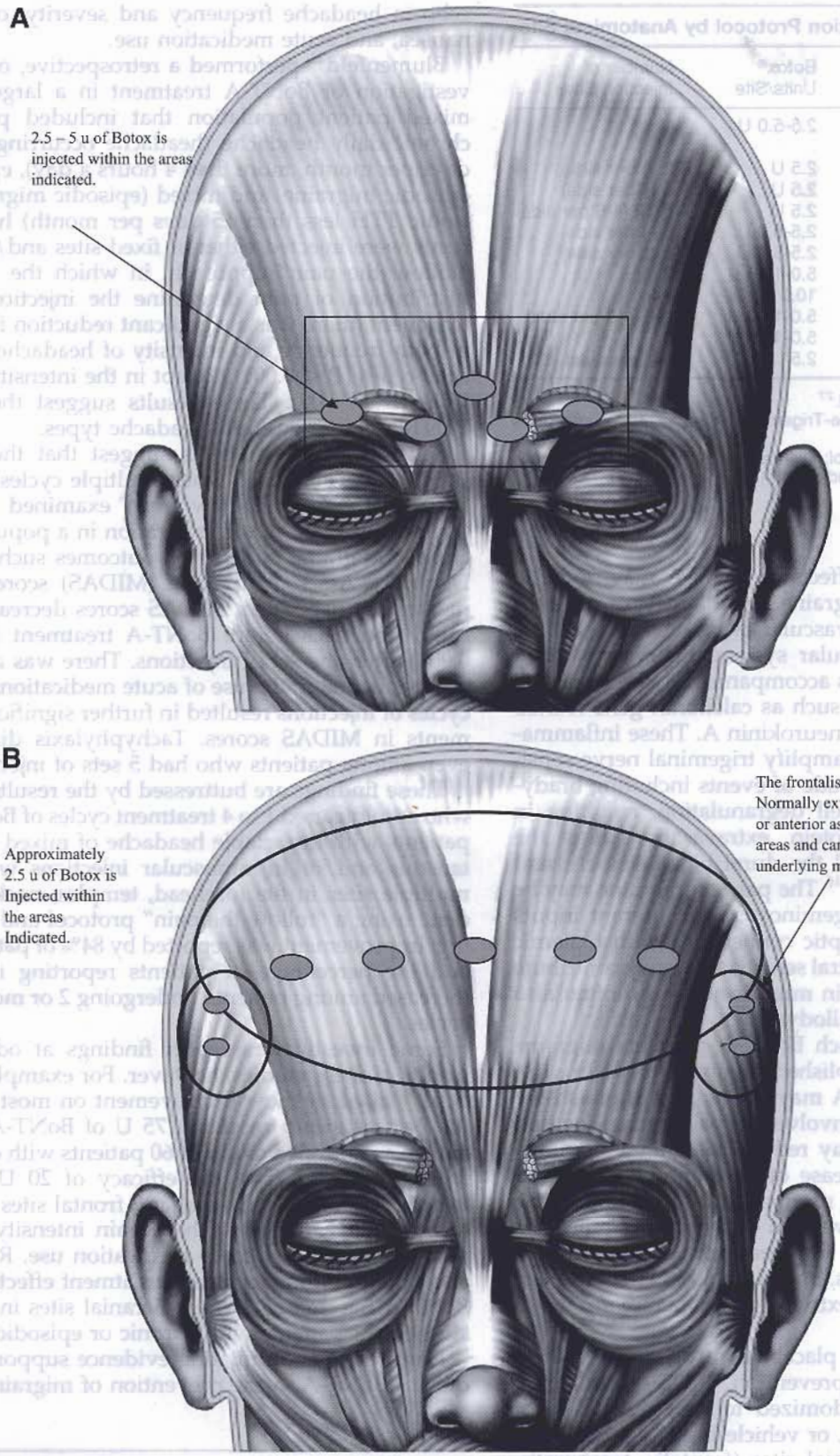

FIGURE 1. (A) Injection sites within the lower medial forehead or glabella area correspond with the corrugator (bilateral) and procerus (midline) muscle groups as well as with the supratrochlear and supraorbital nerves. (B) Areas of injection sites over the forehead, distributed centrally over the frontalis 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 once the needle pierces the skin. The diffusion of the solution injected at each injection site will diffuse over an area ~2 cm in diameter. (Color version of figure is available online.)

mixed headache, negative findings such as these, and the failure of many positive trials to meet the highest evidence-based standards,[25] suggest that much remains to be learned about the factors that maximize treatment response in particular patient populations. For example, variation in dosing or injection regimens across studies may contribute to differences in outcomes.[26] Furthermore, in some studies, insufficient detail about injection methodology is reported, making the outcomes difficult to evaluate. Investigators are beginning to devote more attention to these issues, however, and some trends in their conclusions are emerging.[21,27]

DOSING ISSUES

Two BoNT-A formulations (Botox® and Dysport®) and one type B formulation (Myobloc®) are approved for clinical use, although only Botox® and Myobloc® are available in the U.S. These 3 products have different dosing and safety and efficacy characteristics, and there is no formula for establishing dosage equivalency. Botox® is available in vials containing 100 U of BoNT-A, each of which is typically diluted with 2 or 4 mL of preservative-free 0.9% saline, yielding a preparation of 5.0 or 2.5 U/0.1 mL, respectively. Myobloc® is available in vials containing 2,500 U and 5,000 U of BoNT-B per mL in 0.05% human serum albumin.

Although there is no consensus regarding dose and dilution for BoNT-A injections for migraine, our experience has shown that lower concentrations of BoNT-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. Factors influencing the total dose of BoNT-A, which should be individualized, include type of headache, severity of symptoms, and body size.

INJECTION TECHNIQUE

Injections should be placed intramuscular or in the perimuscular space periosteum. Injections in the forehead region should be bilateral and symmetrical to avoid facial asymmetry; elsewhere, bilateral injections need not be symmetrical. The inferior–lateral frontalis region (lateral suprabrow areas) is best avoided, unless pain is present in this area, to reduce the risk of brow ptosis.

INJECTION SITES AND PROCEDURES

The entire anatomical area affected by pain should be injected with sufficient neurotoxin to achieve a clinical response. In practice, this means injecting the amounts shown in Table 1, with more injection sites used as necessary.[27] Areas typically injected include the glabellar and frontal regions, the temporalis muscle, the occipitalis muscle, and the cervical paraspinal region.

INJECTION PROTOCOLS

The following 3 basic injection protocols are in common use: the "fixed-site" method, the "follow-the-pain" method, and a combination of these.

The "fixed site" method (or "follow-the-trigeminal-nerve") targets fixed trigeminal sites and employs a range of predetermined doses. It is often used for patients with migraine or headaches with migrainous features. Despite the occasionally unilateral quality of some migraines, these patients should receive bilateral symmetrical injections to avoid the development of headache on the other side. Muscles injected most often under this protocol include the procerus, corrugator, frontalis, and temporalis muscles (Figures 3A,B, and 4). If pain is located posteriorly, then the suboccipital areas are targeted as well (Figure 3A). For cosmetic reasons, unilateral facial muscle movement (ie, frontalis muscle) is also an undesirable cosmetic outcome.[21,27] Blumenfeld[27] has obtained good results by using a more extensive version of this protocol, with bilateral injections (except for those in the procerus muscle) of Botox® (100 U/4 mL) at as many as 25 sites.

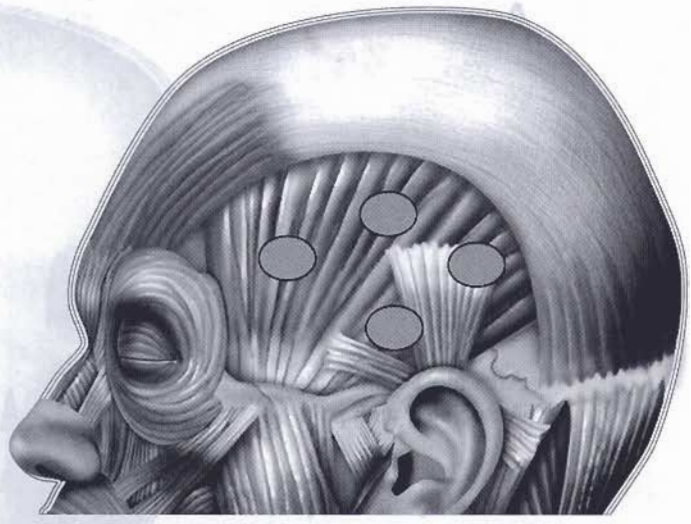

FIGURE 2. The 4 general areas of injection over the region occupied by the temporalis muscle. There are normally 4 to 5 injection sites, with an average dose of 20 to 25 U per side, averaging ~5 U per injection. (Color version of figure is available online.)

The "follow-the-pain" approach is most often used to treat TTH. This is a more individualized approach in which sites and doses are adjusted depending on the distribution of pain and tenderness. Asymmetrical injections are often given. Factors to assess include head and neck position, muscle bulk, and temporomandibular joint function. Muscles most commonly injected include the frontalis, temporalis, occipitalis, splenius capitis, trapezius, and cervical paraspinal muscles (Figure 3). Posterior neck muscle injection sites are similar to those selected for patients experiencing painful cervical dystonia. In other circumstances, pain that can be elicited by palpation should also be injected.

Patients often have coexisting migraine and TTH. A combination approach is appropriate in these cases, and injections at fixed trigeminal sites are supplemented with additional injections to "follow the pain." Doses are generally higher under the combination regimen. Where examination reveals signs of temporomandibular disorder, such as pain around the ear or jaw, with crepitus of the joint, one of the standard headache protocols may be supplemented with a "follow the muscles of mastication" strategy, in which the temporalis and masseter muscles are injected. Finally, cervical dystonia can be a cause of head and neck pain. Where appropriate, a "follow the dystonia" protocol may be employed, with injections at sites in sternocleidomastoid, splenius capitis, levator scapulae, or trapezius muscles. The following important caveat

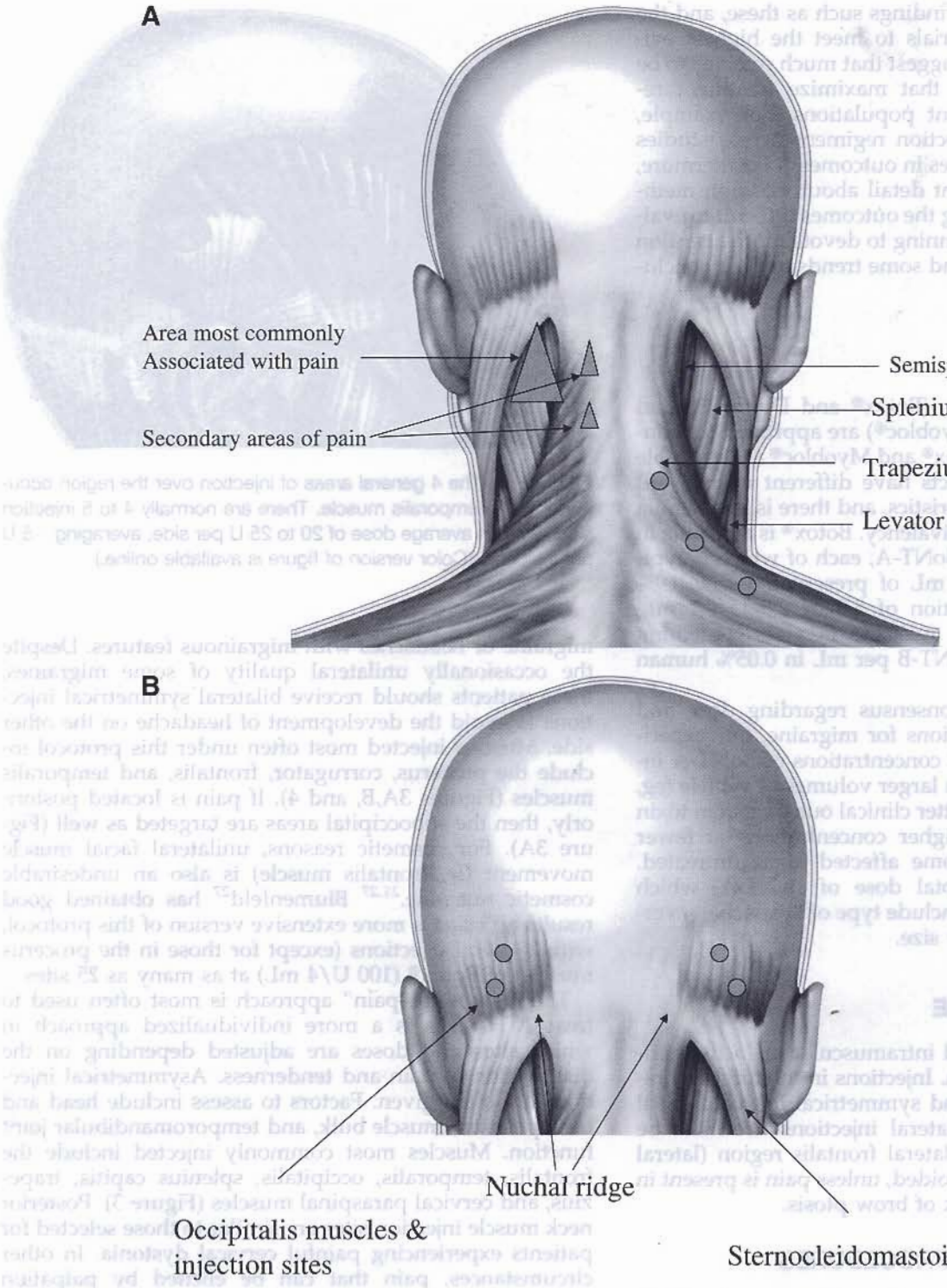

FIGURE 3. (A) Injection sites for the splenius capitis and trapezius muscles. Usually, an area just below the nuchal ridge between the trapezius and sternomastoid muscle is the most common site of pain (arrow). This area is occupied primarily by the splenius capitis muscle. It is important to note that an anatomical overlap exists with respect to the upper portion of the trapezius, rectus capitis, semispinalis capitits, and splenius capitis. Therefore, in this region, it is most important that the injection be administered to the "area" where the pain is greatest, rather than to a particular isolated muscle. One to four sites can be injected with 5 to 20 U per side. (B) Injection site for the occipitalis muscle (the area just above the nuchal ridge). Usually 1 to 2 injection sites of 5 to 7.5 U per side is sufficient. (Color version of figure is available online.)

applies to such cases: the dystonic muscles should be the primary focus of injection. Lower doses should be injected into the painful compensatory muscles to avoid weakening them.

These injection protocols, which are summarized in Table 2, can be used in any combination as warranted.

ANATOMICAL AND TECHNICAL CONSIDERATIONS

Number of injections, dosages, and other aspects of technique will vary by anatomical area. Table 1 gives the number of sites and total Botox® dose appropriate to each area.

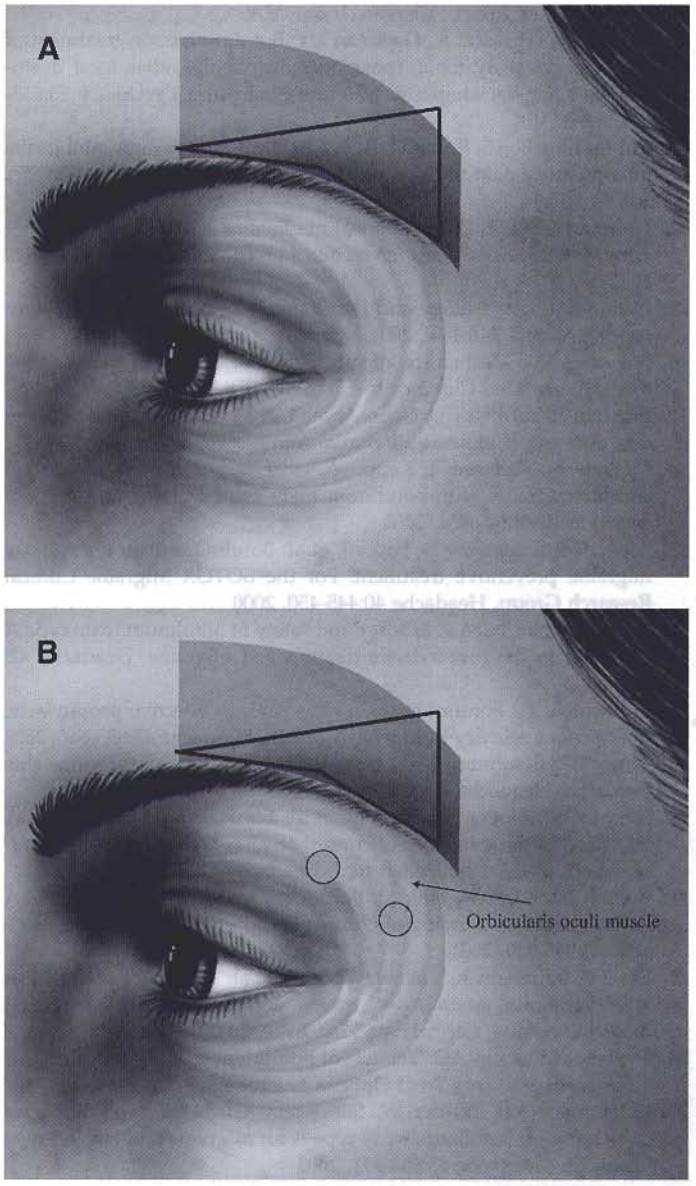

FIGURE 4. (A) The shaded area above the eyebrow represents an area from the mid-pupillary line extending laterally to a point ~1 cm in vertical height over the lateral-most portion of the eyebrow. (B) Injecting the superior lateral aspect of the orbicularis oculi muscle with BoNT-A (2.5-5 U) weakens 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 infero-lateral portion of the frontalis muscle. (Color version of figure is available online.)

Smaller fluid volumes (ie, 0.1-0.2 mL per injection) are injected into the glabellar area, with precise placement and slow injection to prevent dispersion of the toxin to adjacent muscles. When injecting the corrugator muscles, there is a possibility of extravasation of toxin downward into the eyelid, resulting in ptosis. This can be avoided by direct pressure at the border of the supraorbital ridge. The injection sites into the medial and lateral corrugator muscles correlate directly with the supratrochlear and supraorbital nerves (Figure 1A). In the frontalis muscle (forehead region), greater distribution and dispersion of the toxin with larger volumes has led to better outcomes. Injection of the lower third of the frontalis may inhibit the patient's ability to raise the brows. The frontalis region should be injected symmetrically to avoid facial asymmetry (Figure 1B). The area of the forehead over the lateral aspect of the brow should be avoided to prevent brow ptosis (Figure 4A); 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 supero-lateral aspect of the orbicularis oculi muscle (Figure 4B). 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 experience pain in this area, an additional 2.5 to 5 U per side may be injected (Figure 1B).

Large doses may be injected into the temporalis muscle; the large size of this muscle reduces the risk of unintended effects on adjacent muscles. In patients with a history of temporomandibular disorder or occlusal problems, it's important that injections be performed bilaterally and symmetrically. The most anterior aspect of the temporalis muscle can be identified by having patients clench 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 (Figure 2).

If the patient has posterior neck pain, then the occipital or cervical paraspinal areas should be evaluated. Areas associated with pain and tenderness on palpation, typically in the region of the splenius capitis, should be injected. In the posterior suboccipital region, it is normally not necessary to differentiate specific muscles, because the muscles in this region are thin and overlap each other. Rather, choices for injection should be based on the area of pain. The suboccipital area of the neck below the nuchal ridge is occupied mostly by the splenius capitis muscle. Between 1 and 4 sites can be injected with 5 to 20 U per side. The superior portion of the trapezius muscle can also be injected if necessary (1-3 sites per side, 5-15 U). If the inferior part of the trapezius is also tender, it can also be injected (3 sites, 5-15 U; Figure 3A). If the occipitalis muscle is involved above the nuchal ridge, it can be injected as well (Figure 3B).

Most injections are made with a half-inch 30-gauge needle and a 1-cc 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. Regionally, vessels should be palpated to avoid intra-arterial injections, and superficial blood vessels should be visualized to avoid bruising.

ADVERSE EFFECTS AND POSTINJECTION MANAGEMENT

Adverse effects can be minimized through proper injection techniques. When they occur, adverse effects are minimal and transient. Reported effects include blepharoptosis, diplopia, and muscle weakness at injection sites.[19]

Brow ptosis occurs due to infero-lateral frontalis muscle weakness. This can be lessened by orbicularis oculi treatment (Figure 4A,B).

Patients should be advised about the reduction of hyperfunctional facial lines. They should also realize that maximal headache relief usually occurs only after 2 weeks, and that acute medication for breakthrough headaches will be needed. They should be strongly encouraged to keep headache diaries so that the effects of treatment can be evaluated. Repeat injections improve outcomes for many patients. Repeat treatments every 3 to 4 months are required to continue the benefits of therapy.

CONCLUSION

BoNT-A is a promising new treatment option for the prevention of headache. Despite an incomplete understanding of its mechanism for reducing headache pain, a paradigm for its use is emerging, based on the collective experience of clinical investigators. Its use across an array of indications over the last decade has demonstrated an extremely favorable safety and tolerability profile. Small-scale clinically based investigations have also provided an index of its effects on headache symptoms, quality of life, and use of acute medication. We await the results of large, placebo-controlled, double-blinded studies to better understand which patients benefit most from treatment, and which treatment regimens provide the best outcomes.

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