Botulinum Toxin Treatment of Migraine and Other Headaches

Sara M. Schaefer and Bahman Jabbari

Introduction

Headache is a common human ailment. Approximately 47% of the adult population in America is believed to have a headache at least once per year [1].

Over the past 15 years, there have been substantial developments in the pharmacological treatment of primary headaches (migraine and others), but still a large number of patients remain unsatisfied. The International Headache Society has classified headaches into primary and secondary headaches [2].

In this review, we describe common human headaches, their pathophysiology, and current accepted treatment strategies. We then provide data on botulinum toxin treatment of headaches with the focus on primary headache disorders (Table 1) and emphasize the data derived from prospective, double-blind, placebo-controlled studies.

Migraine

Migraine is the most common neurological disorder, and the third most prevalent condition overall in the world, after anemia and hearing loss [3]. In the largest and most recently published epidemiological study of migraine (12,000 participants), the overall prevalence of migraine was 12% (17% among women, 6% among men) [4]. This study noted that chronic migraine causes moderate to severe disability in 78% of women and 66% of men. Migraine headache often has a characteristic throbbing quality, is of moderate to severe intensity, and often affects one side of the head more than the other. Most patients complain of photophobia, phonophobia,

S.M. Schaefer, M.D. • B. Jabbari, M.D., FAAN (✉)
Department of Neurology, Yale University School of Medicine, New Haven, CT, USA
e-mail: Sara.schaefer@yale.edu; Bahman.jabbari@yale.edu

Table 1 Primary Headache Disorders, From International Headache Society Classification of Headache Disorders, 2nd Edition

Type	Subtype	Frequency	Duration	Characteristics	Associated symptoms
Migraine	Chronic	≥15 days per month for >3 months	4–72 h	Unilateral, pulsating, moderate to severe intensity	Photophobia, phonophobia, nausea, vomiting, avoidance of activity, ±aura
Migraine	Episodic	<15 days per month	4–72 h	As above	As above
Tension	Episodic (infrequent or frequent)	<1–15 days per month	30 min to 7 days	Bilateral, non-pulsating, mild to moderate intensity	No photophobia, phonophobia, nausea or vomiting. Not aggravated by routine activity
Tension	Chronic	≥15 days per month	Hours to continuous	As above	As above
Trigeminal autonomic cephalalgia (TAC)	Cluster headache	Every other day to 8 per day, occur in clusters	15–180 min	Unilateral, severe intensity, orbital, supraorbital, and/or temporal	Ipsilateral autonomic symptoms (lacrimation, conjunctival injection, edema, sweating, miosis, ptosis), restlessness
TAC	Paroxysmal hemicrania	3–200 per day	5–240 s	As above	Ipsilateral autonomic symptoms as above
TAC	Short-lasting, unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)	5 per day for more than half the time	2–30 min	Unilateral, severe intensity, orbital, supraorbital and/or temporal, stabbing or pulsating	Ipsilateral conjunctival injection and lacrimation

and/or gastrointestinal distress during the attacks. Those with a severe migraine attack often seek a quiet, dark room because routine activities exacerbate the headache. Migraine may occur with or without aura, the most common of which are visual, sensory, or dysphasic. Episodic migraine is characterized by a headache frequency of less than 15 days per month and chronic migraine with a frequency of 15 or more days per month. The direct and indirect annual costs of migraine have been reported to be as high as $17 billion dollars in the United States in 2005 [5] and 27 billion Euros/year in Europe in 2004 [6].

The pathophysiology of migraine includes a cascade of events that begins with the phenomenon of cortical spreading depression (CSD), travelling across the cortex at a speed of 3–6 mm/s. This electrical phenomenon often involves the occipital cortex, leading to visual aura [7]. During CSD, the release of potassium, nitric oxide, adenosine, and other agents causes inflammation and vasodilation in the cortex and meningeal vessels with consequent sensitization of the trigemino-vascular system (TVS) [8]. Sensitized TVS sends enhanced afferent impulses to the trigeminal ganglion, trigeminal nucleus caudalis, superior salivatory nucleus, and parasympathetic efferent fibers [9]. The release of calcitonin gene-related peptide (CGRP), which corresponds to dural vasodilation, seems to be another major player in the process [10]. Recent studies have demonstrated a potential role of transient receptor potential vanilloid type-1 receptor (TRPV1) and transient receptor potential ankyrin 1 (TRPA1) channels in the pathophysiology of migraine pain. It has been shown that TRPV1 increases in the peri-arterial nerve fibers from scalp artery specimens in migraine patients as compared to controls, irrespective of whether or not the patient had a migraine at the time of sampling, implying a more chronic uptake in TRPV1 receptors among these patients [11]. Cutaneous allodynia during a migraine attack may mark a transition of pain from peripheral to central, since the peripherally activating agents such as triptans are ineffective once patients develop allodynia [12]. Cernuda-Morollon et al. found that, compared to asymptomatic controls, serum levels of calcitonin gene-related peptide (CGRP) are 2.5 times higher in patients with chronic migraine (CM) compared to asymptomatic controls and about 1.8 times higher in patients with episodic migraine (EM) or cluster headaches ($p < 0.05$), identifying a potential biomarker for primary headache disorders [13].

Treatment of migraine consists of abortive and preventive therapy [14, 15]. Mild attacks can be managed by acetaminophen, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs). Triptans are commonly used for more severe attacks. However, one-third of the patients fail triptans, many patients demonstrate poor tolerance, and the presence of cardiovascular co-morbidities is a contraindication [16]. For very severe episodes, administration of dopamine receptor agonists (e.g., prochlorperazine), dihydroergotamine (DHE), and/or intravenous NSAIDs (diclofenac or ketorolac) is recommended, especially when the attacks have surpassed the peripheral phase of activation [17]. In some patients, high flow oxygen may alleviate acute attacks of migraine [18].

Preventive daily treatment of migraine is recommended when migraine episodes exceed 6–8 headache days per month or what is tolerable to the patient, if the patient has to use abortive medications more than 8–9 times per month, or if headache-related disability is significant [19]. Beta-blockers such as propranolol or metoprolol, topiramate, amitriptyline, and divalproex sodium (DVPX) are commonly recommended for preventive treatment of migraine [20]. Newer preventive measures include supraorbital percutaneous electrical stimulation (once daily for 20 min) [21] and transcranial magnetic stimulation [22]; both are now approved by the FDA for the treatment of chronic migraine. Finally, monoclonal antibodies targeted to CGRP and oxytocin nasal spray have both shown promise in relieving chronic migraine in phase 2 studies [23, 24], and are now being evaluated in phase 3 investigations.

Botulinum Toxin Treatment of Migraine Headaches

Botulinum toxins can reduce pain via a variety of peripheral and central mechanisms which reduce the phenomena of peripheral and central sensitizations integral to the pathophysiology of chronic pain syndromes [25]. On the peripheral side, onabotulinumtoxinA inhibits the release of pain peptides, substance P, bradykinin, CGRP, and glutamate from the dorsal root and trigeminal ganglia [26, 27]. Injection of BoNT-A into the ophthalmic division of the trigeminal nerve decreases TRPV1 immunoreactive neurons by reducing TRPV1 trafficking to the plasma membrane, an effect that persists for at least 14 days [28]. Luvisetto et al. have postulated that in the capsaicin model of pain, the reduction in pain with BoNT pretreatment may be due to its downregulation of TRPV1 responsiveness to capsaicin, a TRPV1 agonist [29]. In an acute model of peripherally generated pain (formalin model), injection of both type A and type B toxins into the rat's paw prior to formalin injection alleviates the secondary peak of pain (inflammatory peak) and reduces local inflammation and accumulation of glutamate [30, 31]. Local onabotulinumtoxinA (ona-A) injection impairs sympathetic transmission [32], thus interfering with maintenance of pain by decreasing sympathetic overactivity. Intramuscular injection of ona-A decreases the discharge of muscle spindles, a major sensory input to the spinal cord [33].

Over the past decade, evidence for central effects of BoNTs has accumulated in the literature from a variety of observations. In animal models of diabetic neuropathy, unilateral, peripheral injection of onabotulinumtoxinA alleviates limb pain bilaterally, indicating a central action [34]. Femtomolar concentrations of BoNT type A inhibit membrane sodium channels in rats in both central and peripheral neurons [35]. Following BoNT type A injection into the rat whisker pad, truncated SNAP-25 was detected in the dorsal horn of the trigeminal nucleus caudalis [36] and in the ipsilateral dorsal and ventral horns of the spinal cord and the spinal cord astrocytes following peripheral sciatic nerve injection [37, 38]. Notably, simultaneous administration of colchicine (which inhibits retrograde axonal transport) negates any antinociceptive effect as observed by rat behavior, highlighting the importance of axonal transport on the effects of BoNT type A.

Administration of BoNT-A directly to the C-meningeal nociceptors in the dura inhibits responses to mechanical stimulation, reverses mechanical hypersensitivity, and prevents the development of mechanical hypersensitivity [39]. Chemical stimulation of dura via application of an inflammatory soup leads to a substantial increase of glutamate in trigeminal nuclear caudalis, and electrophysiological recording from this nucleus demonstrates significant neuronal hypersensitivity. Based on this observation, Orinsky proposed that chemical stimulation of the dura during migraine leads to the communication of dural afferents with trigeminal afferents through axon–axon glutamate secretion, resulting in recruitment and stimulation of a large number of trigeminal afferents and central sensitization of the trigeminal system [40].

Botulinum Toxin Treatment of Chronic Migraine

Chronic migraine is defined as a headache with a frequency of 15 or more headache days per month (at least 8 migraine type), and lasting more than 4 h per day for more than 3 months [2]. A pioneering study of BoNT in episodic migraine [41] generated interest in the investigation of BoNT treatment efficacy in all forms of headaches. Results of subsequent studies of BoNT in episodic migraine and chronic daily headaches (CDH) (including a large number of patients with migraine) were for the most part negative, casting some doubt on the efficacy of BoNT therapy for headaches. However, concurrent positive observations with onabotulinumtoxinA, albeit in smaller populations, kept the door open for further studies. In a subset of 228 patients from a large Chronic Daily Headache trial (CDH) (with no subject on prophylactic headache medication), Dodick et al. found a statistically significant difference in pain relief among patients treated with onabotulinumtoxinA compared to placebo at successive time points over 3 months ($p = 0.004$, $p = 0.032$, and $p = 0.023$) [42]. Also, Freitag et al., in a double-blind placebo-controlled study, compared the effect of a fixed-dose (100 units), fixed-site (glabella, frontalis, temporal, trapezius, suboccipital) paradigm treatment with onabotulinumtoxinA (20 patients) with placebo (21 patients) in chronic migraine [43]. All patients with medication overuse were excluded. The primary outcome was the number of migraine episodes. Secondary outcomes consisted of the number of headache days and headache index (HI—a measure of both intensity and frequency). The authors found ona-A statistically superior to placebo for both primary ($p < 0.01$) and secondary outcomes (frequency of pain days: $p = 0.041$ at 4 weeks and $p = 0.046$ at 16 weeks, and HI: $p = 0.003$ at 16 weeks).

In the summer of 2010, the results of two Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT 1 and PREEMPT 2) trials, two class I multicenter studies assessing the efficacy of onabotulinumtoxinA in chronic migraine, were published [44, 45]. Each study assessed approximately 700 subjects, including comparable numbers of subjects with chronic migraine in the toxin and placebo groups, in a 24-week blind arm followed by a 32-week open arm. Both studies comprised of patients with a history of medication overuse. The primary outcome for PREEMPT 1 was the number of headache episodes, and for PREEMPT 2 the number of headache days, evaluated at 24 weeks. A number of secondary outcomes were also evaluated at the 24-week time point, including frequency of moderate/severe headache days and cumulative headache hours. Although PREEMPT 1 did not meet the primary outcome, it met its secondary outcomes. PREEMPT 2 met its primary outcome with a decrease in headache days by 9 in the ona-A compared to 6.7 in the placebo groups ($p < 0.001$). The pooled data from the two studies also showed a significant change from baseline in favor of ona-A regarding the primary and secondary outcome parameters [46]. The FDA considered headache days (used in PREEMPT 2) a better outcome measure than headache episodes (used in PREEMPT 1) for the study of chronic migraine. Consequently, onabotulinumtoxinA was approved for the treatment of chronic migraine in the UK, Canada, and the USA in

2010. Subsequent prospective real-life studies in large numbers of patients confirmed the efficacy of onabotulinumtoxinA in reducing headaches and improving the quality of life in chronic migraine [47].

Comparator Studies of BoNTs and Oral Agents in Chronic Migraine

Botulinum Toxin Versus Topiramate

Two double-blind, placebo-controlled studies, one single center (60 subjects) and one multicenter (59 subjects) compared the relative efficacy, tolerability, and safety of botulinum neurotoxin versus topiramate in chronic migraine [48, 49]. In both studies, the primary endpoint was the Physician Global Assessment. The secondary endpoints included a number of headache days, Headache Impact Test (HIT-6), and Migraine Disability Assessment (MIDAS) scores. In the first study, subjects had no history of medication overuse and received injections at time points 0 and 3 months. Subjects were followed for 9 months. Authors found similar efficacy for onabotulinumtoxinA and topiramate (40.9% and 42.9% respectively) noting at least a 50% reduction in headache days after 9 months. Although nearly all study participants reported at least one adverse effect (AE), more patients in the topiramate group permanently discontinued treatment due to side effects than those in the BoNT group (24.1% versus 7.7%).

The second study had a placebo arm that lasted 3 months, followed by a 14-week open trial [48]. Both therapeutic approaches were effective with no significant difference between the two groups. AEs were mild, and their rate of occurrence was similar in the two groups.

Botulinum Toxin Versus Divalproex Sodium (DVPX)

Blumenfeld et al. explored the efficacy and tolerability of BoNT and DVPX in patients with episodic or chronic migraine [50]. In a single-center, double-blind, prospective trial, 59 subjects received either BoNT plus oral placebo or placebo injections plus DVPX 250 mg twice daily. Subjects received injections at time 0 and at month 3, with evaluations at months 1, 3, 6, and 9. Outcome measures consisted of the reduction in a number of headache days, responder rate (percentage of patients with a $\geq$50% reduction in attack frequency per month), maximum headache severity, and overall headache index (related to a combination of headache frequency and severity). Patients in both groups demonstrated significant improvements in headache frequency and severity as measured by headache days per month, responder rates, Headache Index scores, MIDAS, and HIT-6 scores. Adverse effects occurred more commonly in patients who took DVPX (DVPX 75.8%, BoNT-A 50%, $p = 0.04$), and these patients were more likely to discontinue treatment because of AEs (DVPX 27.6%, BoNT-A 3.3%, $p = 0.012$).

The Issue of Medication Overuse in Chronic Migraine

Silberstein et al. studied a subset of PREEMPT study cohort who had both medication overuse (MO) and chronic migraine (CM) [51]. Of the 1384 patients in the two PREEMPT studies, 65.3% met the criteria for medication overuse. At 24 weeks, the reduction of pain days in MO + CM subjects compared to the placebo group was significant (-8.2 versus -6.2, $p < 0.001$). MO + CM subjects also met many secondary endpoints: frequency of migraine days, frequency of moderate to severe headache days, cumulative headache hours on headache days, headache episodes, migraine episodes, and percentage of patients with severe HIT-6 scores (all $p < 0.05$). The subjects' triptan intake was significantly reduced after ona-A treatment ($p < 0.001$). The authors concluded that treatment with onabotulinumtoxinA is effective in patients with a history of medication overuse and chronic migraine.

Long-Term Efficacy, Safety, and Effects on Quality of Life

Aurora et al. studied the efficacy of botulinum toxin and changes in the quality of life in the PREEMPT study cohort after five cycles of treatment (week 56) [52]. The mean reduction in headache days, migraine days, and moderate to severe headache days was significantly more in the botulinum toxin group compared to placebo ($p < 0.05$). The quality of life, measured by a >5 point increase in HIT-6 scores, also improved by 44% at week 25 and 59% at week 56 in the botulinum toxin group.

In a more recent study, Silberstein et al. reported on the percent of patients with chronic migraine who responded to the onabotulinumtoxinA treatment cycle in the PREEMPT studies [53]. Of 688 patients who received ona-A, 49.3% described more than 50% improvement after the first cycle of treatment, and an additional 11.3% and 10.3% after the second and third cycles of treatment respectively (a total of 70.9% after the third cycle). These data further support that repeat injections in subsequent cycles increase the efficacy of onabotulinumtoxinA in chronic migraine.

Response of Imploding Versus Exploding Migraine to Botulinum Toxin Therapy

In imploding migraine headaches, patients describe experiencing pressure from outside the head (crushed, clamped, or stabbed by an external force). In exploding headaches, headaches are felt as pressure building inside of the head. Jakubowski et al., in a study of 63 patients with chronic migraine, found that 74% of responders had imploding headaches whereas 92% of non-responders described exploding headaches [54].

Techniques of Injection

Currently, onabotulinumtoxinA (Botox, Allergan Inc.) is the only form of BoNT approved by the FDA for the treatment of chronic migraine. A variety of approaches have been employed for the treatment of chronic migraine with onabotulinumtoxinA injections. Almost all investigators advocate the inclusion of the procerus, corrugator, frontalis, temporalis, occipitalis, and posterior cervical muscles as injection sites. Three of these methods which have proven efficacious in blinded studies are described below.

In one of the earliest publications of an injection scheme for BoNT therapy for migraine [55], authors advocated use of five injections (2.5 units) into each side of the frontalis muscle, two injections into each corrugator, and one injection into the procerus muscle at midline (Table 2 and Fig. 1a). A slight modification of this technique was used by Silberstein at Jefferson's Headache Center until 2009 [56]. A total dose of 130–160 units was delivered into 32 injection sites.

The PREEMPT study recommends two injections (5 units) into each side of the frontalis, four injections (5 units each) into each temporalis, three injections (5 units each) into each occipitalis, two 5 unit injections into upper cervical muscles (each side), and three 5 unit injections into the trapezius muscle on each side (Table 2 and Fig. 1b) [57]. This technique uses a total of 31 injection sites and 165 units with expansion to 195 units in special cases.

For the past 12 years, Jabbari and his colleagues at Yale have used a technique that employs fewer temporal injections (two, each 15 units), one occipital injection (5 units), three cervical injections (10 units each), and no shoulder trapezius injections (Table 2 and Fig. 1c). The rationale for fewer temporal injections is that the tendon of the temporalis muscle is large and can extend up to 45 mm vertically from the zygomatic arch [58]. Hence, the lower temporal injection site of PREEMPT (Fig. 1b) may be into the temporalis tendon and not into the muscle in many patients. Furthermore, in the cervical area, if one considers the possible contribution of cervical muscles in migraine, two 5 unit injections in the upper cervical region (PREEMPT) may not produce an optimal effect for such powerful muscles. The Yale technique has the advantage of using fewer injection sites (23 versus 31 in PREEMPT) while using comparable doses (185–195 units). The Yale technique has been evaluated by an open label and a small double-blind study. In the open investigation, 50 subjects with CM reported prospectively their level of satisfaction with BoNT treatment in the Patient Global Impression of Change (PGIC) [59]. After the first injection, 72% of the patient and after the third injection, 85% of the patients reported their chronic migraine as "much improved" (follow-up 2–8 years). Fifty percent of patients discontinued preventive medication and 61% of patients discontinued abortive medication by the 12th month of treatment. Of the 15 patients who had presented to the emergency room for the relief of a severe headache, 73% had no more visits to the emergency room within 1 year of starting treatment. No significant side effects were reported. More recently, the efficacy and safety of this technique was tested in a double-blind, parallel study followed by an open arm [60]. The

Table 2 Comparison of three techniques of ona-A treatment in CM: muscles, doses in units, and number of injections per side

Method	Procerus (midline)	Corrugator	Frontalis	Temporalis	Occipitalis	Splenius/paraspinalis	Trapezius	Masseter
Blumenfeld et al. 2003 [55]; Silberstein 2009 [56] (Fig. 1)	2.5–5 u	2.5 u × 2	2.5 u × 5	2.5–5 u × 4	2.5–5 u × 1	2.5–5 u × 1	2.5 u × 2	2.5–5 u × 1
PREEMPT 2010 [57] (Fig. 1)	5 u	5 u × 1	5 u × 2	5 u × 4	5 u × 3	5 u × 2	5 u × 3	–
Jabbari et al. (Yale) 2016 [60][a] (Fig. 1)	5 u	5 u × 1	5 u × 3	15 u × 2	10 u × 1	10 u × 3	–	–

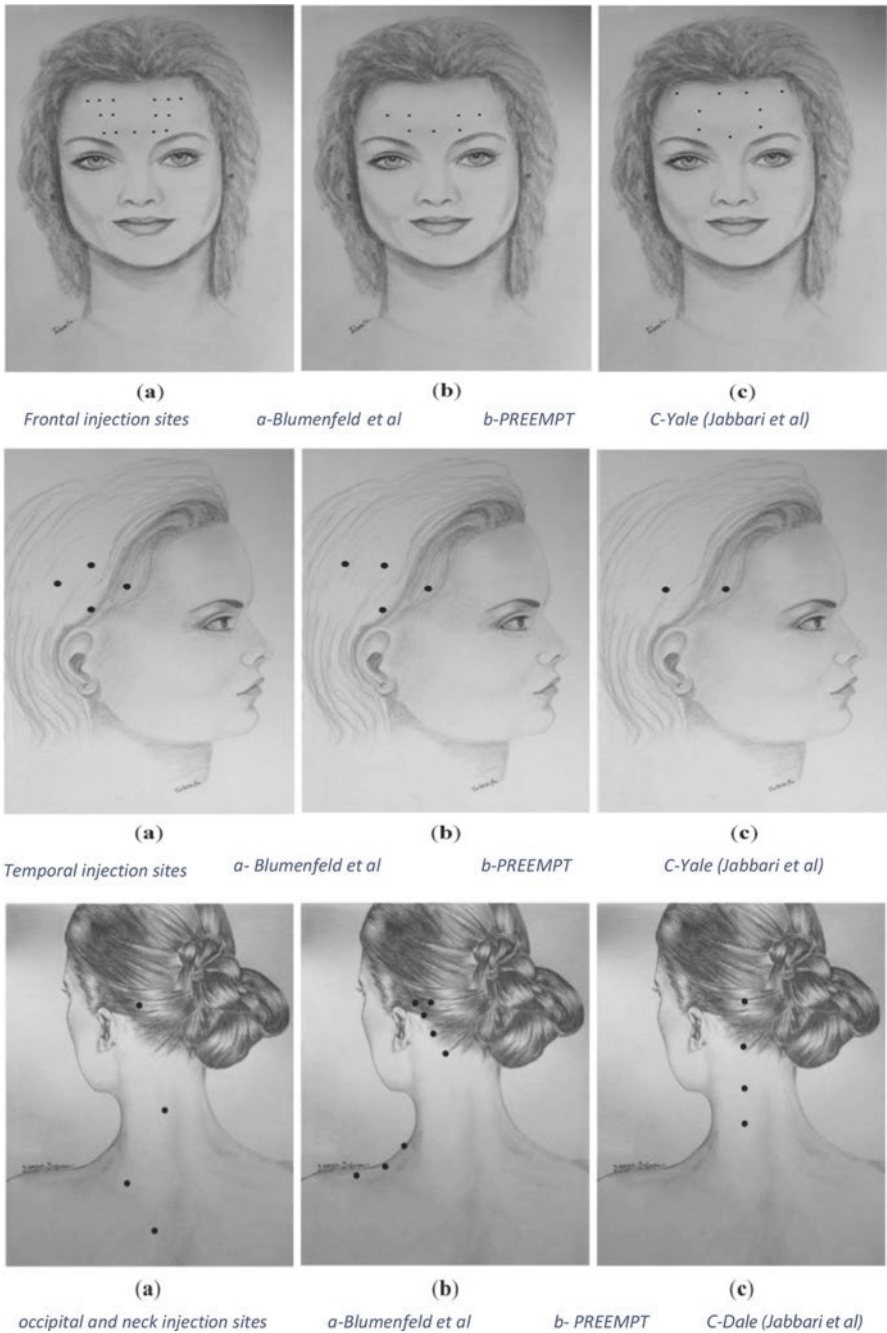[a]There are other neurologists at Yale who use the PREEMPT method for the treatment of migraine

(a)
Frontal injection sites   *a-Blumenfeld et al*   *b-PREEMPT*   *C-Yale (Jabbari et al)*

(b)

(c)

(a)
Temporal injection sites   *a- Blumenfeld et al*   *b-PREEMPT*   *C-Yale (Jabbari et al)*

(b)

(c)

(a)
occipital and neck injection sites   *a-Blumenfeld et al*   *b- PREEMPT*   *C-Dale (Jabbari et al)*

(b)

(c)

Fig. 1 Comparison of three injection methods used for the treatment of chronic migraine with onabotulinumtoxinA. The *top* row represents frontal injection, *middle* row temporal, and *lower* row low posterior (occipital and neck). In each row, the figure on the *left* represents the earlier method produced by Blumenfeld et al., the *middle* figure the one used in the PREEMPT study, and the *right-most* figure the Jabbari/Yale injection protocol. Drs. Tahereh Mousavi and Damoun Safarpour produced the drawing for these figures

blinded arm of the study included 25 subjects, of whom 17 continued in the open-label investigation. The reduction of pain days at 4 weeks (primary outcome) was significantly in favor of onabotulinumtoxinA (6.67 versus 1.20, $p = 0.0347$). With regards to PGIC, 9 of 11 and 3 of 10 patients reported satisfaction with onabotulinumtoxinA and placebo treatment, respectively ($p = 0.030$). In the open arm of the study at 4 weeks, 58.8% reported 50% or more reduction of pain and 88.2% of those treated with onabotulinumtoxinA demonstrated reduction of HIT scores compared to baseline. Table 2 compares the three aforementioned techniques regarding dose and injected muscles.

Episodic Migraine (EM)

In the year 2000, Silberstein et al. published the results of the first double-blind, placebo-controlled, prospective study (class II) investigating the efficacy of onabotulinumtoxinA (ona-A) in 123 patients with episodic migraine (<15 headaches per month) [41]. The study had 3 arms: ona-A 25 units, ona-A 75 units, and placebo. In the 25 unit group, ona A was injected into the procerus muscle (3 units) and bilaterally into corrugators (two on each side, 6 units), frontalis (two on each side, 6 units), and temporalis (one on each side, 6 units) muscles. In the 75 unit group, the dose injected into these sites was 9, 18, 18, and 8 units respectively. The primary efficacy outcome, a significant change from the baseline of migraine attacks, was not met. However, at 3 months, subjects who were injected with 25 units demonstrated significant reduction in headache frequency, headache intensity, and 50% reduction of headaches compared to baseline.

Another class II study of 60 subjects with EM that considered 50% or more reduction of migraine frequency as the primary outcome also failed to meet its primary endpoint [61]. Subsequently, two large class I studies were conducted with onabotulinumtoxinA on 238 and 418 subjects with EM [62, 63]. Both studies failed to meet their primary outcome measure—reduction of migraine frequency. The total dose applied in the aforementioned two studies was 25 and 100 units. Finally, two more class I studies were published which investigated the results of larger doses of onabotulinumtoxinA in episodic migraine [64, 65]. The first study [64] compared the effect of different doses of ona-A (75, 150, and 225 units) to placebo using the mean number of migraine days at day 180 as the primary outcome measure. All four groups (including the placebo group) improved with either ona-A or saline (the placebo) and there was no significant difference between ona-A subgroups and the placebo group. In the second study [65], authors compared the effect of ona-A (mean of 190.5 units) with placebo in 369 subjects. The primary endpoint, defined as the mean change in migraine episodes over 30 days prior to day 180, was not met. Although the study failed to meet the primary endpoint, a subgroup analysis of patients with 12–14 headache days per month showed significant improvement in the ona-A group versus placebo ($p = 0.04$).

Comment

The PREEMPT study data published in 2010 showed the efficacy of onabotulinum-toxinA in chronic migraine, a finding that agrees with the consensus view of experienced clinicians in this field. In the subsequent 6 years, efforts of PREEMPT investigators produced additional data from the large PREEMPT cohort, which demonstrated long-term safety and efficacy of onabotulinumtoxinA in chronic migraine and improved efficacy as well as the quality of life with repeated injections. The most recent report of the Guideline Development Subcommittee of the American Academy of Neurology (2016) [66] designated a level A (established) efficacy for onabotulinumtoxinA in chronic migraine regarding the reduction of headache days per month and a level B (probably effective) in improving the quality of life. A level C (ineffective) was given to onabotulinumtoxinA for episodic migraine.

Tension Headache

Tension-type headaches (TTH) are the most common type of primary headaches with an annual prevalence of approximately 38% [67]. Compared to migraine, tension headaches are more often bilateral, more often have scalp tenderness, and are less often associated with nausea and photophobia [68]. TTHs are not usually as severe as migraine, but severe episodes lead to loss of work days in 8–10% of the affected individuals. Chronic tension headaches (>15 per month) have the same prevalence as chronic migraine (2%) in the general population [69].

It is currently believed that TTHs result from a multifactorial process with contributions from psychological factors, muscle tension, and central processes. Diamond and Dalessio proposed a cascade of events in the pathophysiology of TTHs starting with peripheral muscle contractions that then polysynaptically activate thalamic and cortical neurons via a spinal reflex. Excitation of cortical neurons in turn leads to activation of the descending reticulospinal system, which causes increased muscle tone and muscle contraction through the gamma loop-muscle spindle activation [70].

The mainstays of treatment for episodic tension-type headaches are non-steroidal anti-inflammatory drugs; paracetamol may also be used. For chronic tension headaches, tricyclic antidepressants (especially amitriptyline) are recommended [69]. European guidelines also recommend administration of serotonin/norepinephrine reuptake inhibitors venlafaxine and mirtazapine [71].

Botulinum Toxin Treatment of Tension-Type Headaches

Seven prospective double-blind, placebo-controlled studies have investigated the efficacy of BoNTs in TTH [72–78]. Three studies were class I [75–77] and 4 were class II (Table 3) [72–74]. None but a small class II study met the study's primary

Table 3 Placebo-controlled botulinum toxin studies in tension-type headaches (TTH)

Author	BoNT	Class	Number of patients	Dose (units)	POM	Results	Comments and limitations
Schmidt et al. 2001 [72]	ona-A	II	60	20	WHYPI HD days	Negative	Low dose, limited injected areas
Rollnik et al. 2002 [73]	ona-A	II	21	200	VAS, HD days	Negative	Low dose, mixed chronic and episodic
Shulte-Muttler et al. 2004 [75]	abo-A	I	60	250	Area under curve	Negative	Low dose
Padberg et al. 2004 [74]	ona-A	II	40	100	VAS, HD days	Negative	Low dose, limited injected areas
Silberstein et al. 2008 [76]	ona-A	I	300	50, 100, 150	HD free days	Negative/ positive	POM too rigid
Straube et al. 2008 [77]	abo-A	I	120	210/420	HD free days	Negative	POM too rigid
Hamdy et al. 2009 [78]	ona-A	II	28	50	HD days, VAS, QoL	Positive	Small sample size

VAS visual analog scale, *POM* primary outcome measure, *WHYPI* West Haven Yale Pain Inventory, *HD* Headache, *QoL* quality of life

outcome measure [78]. However, there are major issues with interpretation of the results of these studies regarding the efficacy of BoNTs in TTHs. If one uses the PREEMPT studies of chronic migraine as a model for successful treatment of headache, none of the seven studies meet the dose/technique/primary outcome criteria of PREEMPT. All seven used doses smaller (and sometimes much smaller) than PREEMPT (which used 165–195 units of ona-A). All employed fewer numbers of injections. Three studies (Table 3) used reduction of pain days as the primary outcome (similar to PREEMPT 2), but all three had employed smaller doses and fewer numbers of injections. Interestingly, in a study of TTH by Silberstein et al. [76] the number of pain days (the outcome measure of PREEMPT 2)—which was not the primary outcome measure of their study—was significantly reduced in the toxin-injected group compared to the placebo group ($p = 0.03$). Recently, Harden et al. [79] studied subjects with TTH secondary to cervical myofascial disease with trigger points. Injection of ona-A into cervical trigger points decreased chronic TTH days in the ona-A group ($p = 0.03$), but had no effect on the pain intensity.

We strongly believe that the design of the reported clinical trials in TTHs is sub-optimal and the final word on the efficacy of BoNTs in TTHs awaits conduction of a multicenter study using the technique, dosing, and primary outcome measures similar to a study design which has already shown efficacy in one form of severe headaches (migraine)—for example, that used in the PREEMPT or Yale studies.

Trigeminal Autonomic Cephalalgias [80]

Trigeminal autonomic cephalalgias (TAC) are pain disorders characterized by uni-lateral orbital, supraorbital, and/or temporal pain that may be stabbing or pulsating, associated with ipsilateral autonomic symptoms. The symptoms consist of conjunc-tival injection, lacrimation, edema, diaphoresis, miosis, ptosis, and nasal conges-tion. The subclassifications of these disorders are largely based on duration and frequency of attacks (Table 1). This group includes cluster headaches, paroxysmal hemicranias, short-lasting unilateral neuralgiform headache attacks with conjuncti-val injection and tearing (SUNCT), and short-lasting unilateral neuralgiform head-ache attacks with cranial, autonomic dysfunction (SUNA).

The autonomic dysfunction seen in TAC syndromes is thought to arise from the trigeminal-autonomic reflex. This reflex extends from the pain fibers of the trigeminal nerve through the trigeminal ganglion, descending to the brainstem and trigeminocer-vical complex, and resulting in activation and outflow of parasympathetic fibers [81]. The ipsilateral hypothalamus is the major central site for this reflex (Fig. 2) [80].
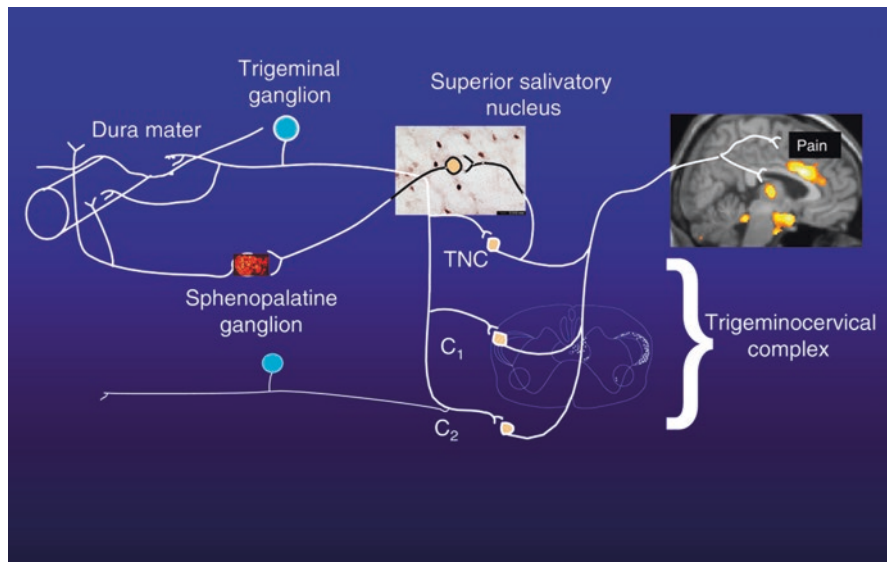

Fig. 2 The anatomy of trigeminal autonomic reflex. From Eller and Goadsby [80], printed from Oral Disease with permission from Wiley and Sons Publisher

First-line therapy for acute cluster headache includes 100% oxygen, at the rate of 6–12 l/min for at least 15 min using a non-rebreather mask, in combination with injectable triptans [82, 83]. Second-line treatments with less compelling data to support their use include ipsilateral intranasal lidocaine and DHE. Verapamil is the best studied prophylactic agent for cluster headaches, with proven efficacy in a randomized, placebo-controlled, double-blinded trial. The patient should start verapamil at a dose of 40–80 mg three times daily, with an increase of 80 mg every week to a target dose of 120 mg three times daily (360 mg per day, total). The main side effects are cardiac arrhythmias; patients should be followed with serial electrocardiograms (ECGs) during therapy. Lithium may be used separately or as an adjunct to verapamil, though the data are less compelling. Topiramate may also be useful for prophylaxis. Other prophylactic agents such as melatonin, valproate, gabapentin, levetiracetam, and baclofen have been tried, but with small sample sizes, and require further investigation [84]. Paroxysmal hemicrania and hemicrania continua (Table 1) respond well to indomethacin but gastrointestinal side effects sometimes limit its use. COX-2 inhibitors may be used as an alternative. Lamotrigine is a first-line drug for patients with SUNCT or SUNA [85].

In refractory cases, resectional and ablative surgeries and neurostimulation have been tried in cluster headache patients [84]. Trigeminal nerve root resection has caused many surgical complications, and has been replaced by gamma knife radiosurgery of the trigeminal and sphenopalatine ganglia. Results have been mixed, with high complication and pain recurrence rates. Occipital nerve and sphenopalatine ganglion stimulation are safer procedures that are gaining traction in refractory populations. As the hypothalamus is a major site in TACs' reflex arc, deep brain stimulation of this site has been explored with promising results. In a recent review of 69 patients (mostly cluster headaches), published in 2015, approximately 70% of patients reported >50% improvement of TAC over 2 years of follow-up [86]. Despite its effectiveness, morbidity and mortality associated with stimulation of this site is a cause for concern [85].

Botulinum Toxin Treatment of Trigeminal Autonomic Cephalalgias (TAC)

A limited number of case reports and open trials claim efficacy of facial and periocular injections of BoNTs in refractory cases of trigeminal autonomic cephalalgias. To date, there are no reports of any blinded and placebo-controlled clinical trials in this area.

Cluster Headaches (CH)

Sostak et al. [87], in an open-label investigation, studied the effect of onabotulinumtoxinA in 12 subjects with cluster headaches who failed preventive medications. Each patient was injected with a total of 50 units of onabotulinumtoxinA ipsilaterally

into frontalis, temporalis, cervical splenius, and trapezius muscles. Three out of nine patients with chronic CH improved significantly after ona-A injections. In one subject, the attacks totally ceased for 18 months. None of the three patients with episodic CH improved, however.

Bratbak et al. [88] injected 25 units of onabotulinumtoxinA in each sphenopalatine ganglion of ten patients with refractory cluster headaches. The main efficacy outcome was the number of CH attacks, which dropped significantly at weeks 3 and 4 after injection ($p = 0.038$). One patient experienced a severe adverse effect—posterior epistaxis.

Hemicrania Continua (HC)

In an open label study, nine subjects with hemicrania continua, unresponsive to indomethacin and other treatments, were injected with onabotulinumtoxinA using the PREEMPT dose/design protocol [89]. Five patients who demonstrated 50% or more reduction of headache days were classified as responders. The median reduction of total headache days was 90% ($p = 0.026$), and for moderate to severe headache days, the reduction was 80% ($p = 0.012$). HIT-6 showed a median change of 12 points ($p = 0.069$). These results suggest the usefulness of onA treatment in HC.

SUNCT and SUNA

Significant improvement of SUNCT after injection of onabotulinumtoxinA has been reported in two case reports [89, 90]. Zabalza [89] treated a 55-year-old man with a 20-year history of severe orbital and periorbital pain associated with redness of the eye and rhinorrhea with the right periocular injection of onabotulinumtoxinA. Four sites were injected, each with 10 units. The patient had failed to respond to a long list of medications including lamotrigine and gabapentin. He was experiencing 20–30 episodes of pain each day with the intensity of 8–10 on a visual analog scale (VAS). After injections, the frequency of pain dropped down to 8–10 per week and the intensity was reduced to 2–3 on VAS. Improvement continued with quarterly injections over a follow-up period of 2.5 years.

Zhan et al. [90] reported a 12-year-old boy with severe episodes of pain affecting the left eye, left upper gums, and the left temporal area. The pain was refractory to the SUNCT conventional pharmacotherapeutic agents. The authors injected the left periocular region, left temporal, and left upper gum at multiple sites, 2.5–5 units/site for a total dose of 70 units. The pain was significantly diminished at day 4 and stopped at day 7 after BoNT injection. All SUNCT medications were discontinued at day 11. The child continued to do well over 17 months.

Comment

The recently published open studies and case observations describing the improvement of refractory TACs with onabotulinumtoxinA therapy are encouraging. Proof of efficacy of BoNT treatment for this form of headaches awaits conduction of clinical trials in a sizeable number of patients, but the low prevalence of TACs makes conduction of large clinical trials difficult. The optimal technique of injection and optimum dose remains to be determined which will most likely differ from those used in migraine due to the more localized nature of pain in trigeminal autonomic cephalalgias.

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