Botulinum Therapy for Chronic Migraine

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ABSTRACT

Chronic migraine (CM) is an important cause of chronic daily headache (CDH), a common severe headache syndrome. Patients with CM are significantly disabled from employment and overuse pain relieving medications. CM is a difficult condition to treat. Overuse of abortive medications and limited benefit from oral preventive medications are an important problem in managing this condition. Recent randomized controlled trials evaluating the efficacy of botulinum toxin A (BoNT-A) have confirmed its efficacy for CM prophylaxis. BoNT-A is a safe drug with no systemic reactions in clinical trials for headache.

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Chronic daily headache (CDH) is defined as a headache that occurs 15 or more days a month for more than 3 months.[1] Chronic migraine (CM), which used to be called transform migraine (TM), is an important cause of CDH.[2] Diagnosis requires at least 8 headache days per month that meet the criteria for migraine without aura or that respond to migraine-specific treatment and the condition should be excluded from medication overuse headache (MOH). Revised International Headache Society criteria for CM are shown in Table 1.[3]

Systematic review in 12 population-based studies revealed the prevalence of CM ranged from 0.9% to 5.1% in general population.[4] These patients are significantly disabled from employment, have psychiatric comorbidities, and overuse acute pain medications.[2,5] Although patients with CM seek medical care, only 20.2% of them have been labeled with a diagnosis of CM, CDH, or TM.[6]

The use of oral prophylactic medications is often limited due to adverse effects. Migraine prophylaxis requires long-term therapy. Thus, an effective, tolerable, and safe treatment is required.[7] BoNT-A is a choice of prophylactic therapy for patients with CM including patients who have failed with oral preventive therapy and patients with medication overuse.[8] For more than two decades, BoNT-A has been successfully used for a variety of conditions associated with increased muscle tone, such as dystonia and spasticity.[2,9] Several evidences support that BoNT-A administration is effective and safe for prophylactic treatment of migraine headache and CDH.[10]

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Pathophysiology of CM

There are many hypotheses for the pathophysiology of CM. Recent research studies in the last 15 years have greatly improved our understanding of the pathophysiology of CM and contributed to the advancement of prophylactic therapy.[11] Accumulating evidences suggest that structural, physiological, and pharmacological changes occur in the brains of patients with chronic, progressive migraine headaches.[11] Structural changes in CM include reduced areas of cortical gray matter in several brain regions involved in pain processing[12] and iron accumulation in the periaqueductal gray matter, red nucleus, and basal ganglia structures.[13] Physiological changes in CM are altered excitability, central sensitization of nociceptive pathways, and brain metabolism which have been confirmed by positron emission tomography studies.[11] Areas of decreased metabolism were found in the medial frontal, parietal, somatosensory cortices, and caudate nucleus, whereas increased metabolism in the pons and right temporal cortex were reported.[14] Alterations in central glutamate neurotransmission have been demonstrated in anterior cingulate and insula using magnetic resonance spectroscopy.[15]

Botulinum toxin: Mechanism of action

BoNT is a potent toxin produced by *Clostridium botulinum*. There are seven serotypes (A-G).[2] It is an approximately 150-kDa polypeptide that consists of two subunits, a light chain (Lc) and a heavy chain (Hc), linked by a disulfide bond. This toxin binds to the target nerve terminal through its Hc domain, and is internalized into an intracellular vesicle. The disulfide bond is then cleaved, and the Lc undergoes translocation to the cytosol. In the final stage, the Lc cleaves one or more proteins involved in neurotransmitter release. The type of protein that is cleaved depends on the toxin serotype. BoNT-A cleaves a synaptosomal associated protein of 25 kDa (SNAP-25),

TABLE 1. Revised International Headache Society criteria for chronic migraine.

A.	Headache (tension-type and/or migraine) on ≥ 15 days per months for at least 3 months
B.	Occurring in a patient who has had at least five attacks fulfilling criteria for migraine without aura
C.	On ≥ 8 days per month for at least 3 months headache has fulfilled C.1 and/or C.2 below, that is, has fulfilled criteria for pain and associated symptoms of migraine without aura
	1. Has at least two of a-d
	(a) unilateral location
	(b) pulsating quality
	(c) moderate or severe pain intensity
	(d) aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
	and at least one of a or b
	(a) nausea and/or vomiting
	(b) photophobia or phonophobia
	2. Treated and relieved by triptan(s) or ergot before the expected development of C.1 above
D.	No medication overuse and not attributed to another causative disorder.

whereas BoNT-B attacks a vesicle associated membrane protein (VAMP), also called synaptobrevin. The result is the prevention of synaptic vesicle fusion with the plasma membrane and, thus, of neurotransmitter release.[16,17] This property makes it useful for many conditions which involve excessive muscle contractions, such as cervical dystonia and spasticity.[18] There are many evidences which support the analgesic effect of BoNT-A, independent of its muscle relaxation effect.[2] Clinical observations are that some patients with dystonia obtain pain relief before experiencing improvement in muscle tone[17] and pain relief has been observed in areas where no reduction of muscle contraction occurs.[19] BoNT-A also was found to alleviate migraine headaches in some patients who were given the toxin to treat hyperfunctional lines of the face.[20] These observations led to intense efforts to evaluate the analgesic properties of BoNT-A. Cui et al discovered that subcutaneous administration of BoNT-A inhibited formalin-induced inflammatory pain in rats.[21] BoNT-A has been found to inhibit calcium-dependent substance P secretion from culture embryonic dorsal root ganglion neurons[22] and inhibit calcitonin gene-related peptide (CGRP) secretion from stimulated trigeminal neurons.[23] Based on these studies, BoNT-A inhibits neurogenic inflammation by attenuation of the release of neuropeptide transmitters, and this results in the inhibition of peripheral sensitization.[24]

BoNT-A for CM: Evidence from clinical studies

Evidence from 8 randomized-controlled trials (RCTs) does not support the efficacy of BTA (BTA has not yet been defined) for the prophylaxis of episodic migraine.[25] There are several studies which have evaluated the effect of botulinum toxin A in patients with CDH. These studies included patients with CDH of various causes, and the most common subtypes were chronic tension type headache and CM. Few studies evaluated only patient with CM. The injection protocols commonly used are the fixed-site approach, follow-the-pain approach and combination approach. Injecting specifically into muscular trigger points has proved effective.[26] The dose of BoNT-A was varied between studies. The result of these studies in terms of efficacy for CM prophylaxis were mixed.[27,28,29]

Freitag et al evaluated the efficacy of BoNT-A in treating CM without medication overuse. The study included 41 patients who were randomized to BoNT-A or placebo injection. BoNT-A was injected into cranial muscles using a fixed dose and site paradigm, at a total dose of 100 U. BoNT-A was statistically superior to placebo for the primary endpoint of reduction in migraine headache episodes (-31% vs. -9% migraine episodes per month).[27]

Two large multicenter, double-blind, randomized, controlled studies: PREEMPT (The Phase III REsearch Evaluating Migraine Prophylaxis Therapy) 1 and 2,[28,29] assessed the efficacy, safety and tolerability of BoNT-A as a headache prophylaxis in adults with CM. In PREEMPT 1, there were 679 patients randomized to BoNT-A or placebo injection every 12 weeks. These studies included patients who were overusing acute pain medications and excluded patients who used any headache prophylactic medication within 28 days before starting the study. BoNT-A 155U or placebo was administered in fixed-sites, across specific head and neck muscle areas. An additional 40U could be administered into the muscles follow-the-pain strategy according to the investigator's decision. The primary endpoint, which was the mean change from baseline in frequency of headache episodes at week 24, revealed no significant difference between groups. However, BoNT-A was significantly superior to placebo in several secondary outcome measures, including decrease of headache days (-7.8 vs. -6.4, p=.006), migraine days (-7.6 vs. -6.1, p=.002), decrease in disability and improved functioning as measured by the mean change in total Six-questions Headache Impact Test (HIT-6) score. However, the study was limited by baseline imbalance, because patients receiving BoNT-A had significantly fewer headache episodes and migraine episodes than patients receiving placebo, but significantly more cumulative hours of headache occurring on headache days. PREEMPT 2 included 705 patients with chronic migraine. The criteria for patient selection, injection paradigm and duration of double-blind phase were similar to the PREEMPT 1 study. PREEMPT 2, baseline patient demographics and headache characteristics were similar between the treatment groups. The primary endpoint was the mean change from baseline in the number of headache days at week 24, rather than frequency of headache episodes. The BoNT-A group was significantly decreased with a mean change in number of headache days (-9.0 days BoNT-A versus -6.7 days placebo, p<.001). The BoNT-A group was superior to placebo with regard to the secondary end point which was the frequency of migraine days, frequency of moderate/severe headache days, total monthly cumulative hours of headache occurring on headache days, proportion of patients with severe HIT-6 scores and frequency of headache episodes. The BoNT-A significantly reduced the disability and improved

the quality of life and was well tolerated.

Roger K, et al evaluated the efficacy of BoNT-A compared with topiramate for CM prophylaxis, and 59 patients were randomized into 2 groups, 30 received 100-200 mg topiramate plus placebo injections and 29 received 100-200 units BoNT-A injections plus placebo tablets. One hundred units of BoNT-A was injected into fixed locations and up to an additional 100 units in a follow the pain scheme determined at the investigators discretion. The primary endpoint, improvement of 'The Treatment Responder Rate' based on the Physician Global Assessment, was no significant between groups.[30]

Safety and tolerability

More than two decades of clinical use has demonstrated the remarkable safety of BoNT-A and no serious allergic reactions have ever been reported, although rash and flu-like symptoms can rarely occur. Injection of the anterior neck muscle can cause dysphagia in a small number of patients.[31] BoNT-A should be used with caution for patients with neuromuscular junction diseases (e.g. myasthenia gravis) and is contraindicated for patients who take aminoglycosides.[32] It is not recommended for use in pregnant and lactating woman, since there is not enough data yet on the safety.

CONCLUSION

CM is a severe headache syndrome and not uncommon in the general population. These patients often are disabled and complicated by overuse of pain medications. The mechanism of action of BoNT-A is the inhibition of acetylcholine exocytosis through cleavage of SNAP-25, which results in muscle relaxation. However, there are many evidences from both clinical observations and clinical studies which support the use of BoNT-A as an analgesic. Evidence from many RCTs does not support the efficacy of BoNT-A for the prophylaxis of episodic migraine. For CM prophylaxis, the results were mixed. However, recent studies have supported the efficacy of BoNT-A for CM prophylaxis. It requires further studies to gain better evidence of BoNT-A for CM prophylaxis and identify the predictors of response to this drug.

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