Botulinum Toxin in Chronic Migraine Treatment

Subjects: Clinical Neurology

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Primary headaches are a large group of diseases where the headache is not a symptom of another known disease. Tension-type headache affects approximately 80% of the general population, and the prevalence of migraine is estimated at 10–12%. Clinical data and experience to date have demonstrated that botulinum toxin may be an effective prophylactic treatment for chronic headache types. It has been used in neurology for the treatment of dystonia and blepharospasm. Now it has been approved to treat chronic migraine and has been shown to confer significant benefit in refractory cases. Botulinum toxin is effective in pain control through its interaction with the SNARE complex, which inhibits the release of neurotransmitters, such as glutamate, substance P and calcitonin gene-related peptide. OnabotulinumtoxinA is effective not only in headache frequency and pain intensity but in other parameters, including quality of life.

Keywords: chronic migraine ; onabotulinumtoxinA ; headaches ; botulinum toxin

1. Introduction

Headaches are a very common condition that most people will experience many times during their lives. The World Health Organization (WHO) estimated that almost half of all adults will have experienced at least one headache within the last year. There are several kinds of headaches caused by various factors such as the environment, the medication we take and other causes. The International Classification of Headache Disorders 3rd edition (ICHD-3) defines more than 150 different types of headaches, which it divides into two main categories: primary and secondary [1]. The primary headaches, otherwise named idiopathic, are a large group of diseases and syndromes in which the etiology is unclear, and the headache is not a symptom of another known disease. The most common of these are migraines, tension-type headaches and trigeminal autonomic cephalalgias. On the other hand, secondary headaches may be a symptom of a serious underlying medical condition [2].

Migraines are highly prevalent. As a chronic disease, it is the third most common and the seventh most disabling illness globally in people under 50 years old [3]. Only correct diagnosis and effective treatment positively affect a patient's quality of life. Chronic migraine (CM) is defined by the current ICHD- 3 as a headache occurring on ≥15 days per month for 3 months with features of migraine on ≥8 days/month and is a disabling condition that effects 0.5% to 5% of the general population [1]. The progression of episodic migraine to chronic migraine is a complex mechanism that is not fully understood. However, known modifiable risk factors for the progression include the frequency of headache attacks, stressful life events and ineffective acute treatment [4].

There are many treatment options available to help manage the pain. Pharmacologic management for primary headaches includes both: acute and prophylactic treatment strategies. However, it often observed considerable side effects with these therapies, which, unfortunately, limits their usefulness. In patients who take medications too often to treat their headaches, MOH—Medication Overuse Headache—may occur. It is also known as a rebound headache. These can cause migraine episodes to occur more frequently and become more severe. Instead of alleviating symptoms, the medications increase the intensity and frequency of headaches [5]. Migraines, if it is not effectively managed, can lead to significant disability. The primary goals of migraine treatment include relieving the pain, reducing headache frequency and preventing progression to chronic migraine.

Migraines are often refractory to medical therapy and may respond well to onabotulinum toxin (ONABoNTA). ONA-BoNTA is used in neurology for the treatment of dystonia and blepharospasm. Now ONA-BoNTA injections are approved for preventing chronic migraines. The clinical efficacy of botulinum toxin serotype A has been shown in two phase III, placebo-controlled trials (PREEMPT 1 and PREEMPT 2) [6][7]. Based on the phase III program, the number of headache days per month was significantly lower. Significant reductions in the frequency of headache days, headache episodes and triptane use were observed. In summary, OnabotulinumtoxinA positively influenced quality of life and had an acceptable safety profile.

2. Botulinum Toxin in the Management of Chronic Migraine

According to the ICHD-3, the diagnosis of chronic migraine was mentioned above. Moreover, the diagnosis of chronic migraine is based on the patient's history (including a headache diary) and neurological examination. To rule out secondary causes for headaches, magnetic resonance of the brain and lumbar puncture may be necessary. The main goal in the treatment of chronic migraine is to reduce the impact of migraines on patients' lives [8]. It is very important to keep migraine attacks as rare, short and as least impairing as possible. There are two pillars for the treatment of chronic migraine: treatment of acute attacks and prophylactic treatment. Due to the risk of MOH, prophylactic treatment is important in this group of patients. The overuse of headache medications can be a problem for patients with chronic headache disorders. One of the substances approved by the United States Food and Drug Administration for the treatment of CM, as mentioned before, is ONA-BoNTA [9][10].

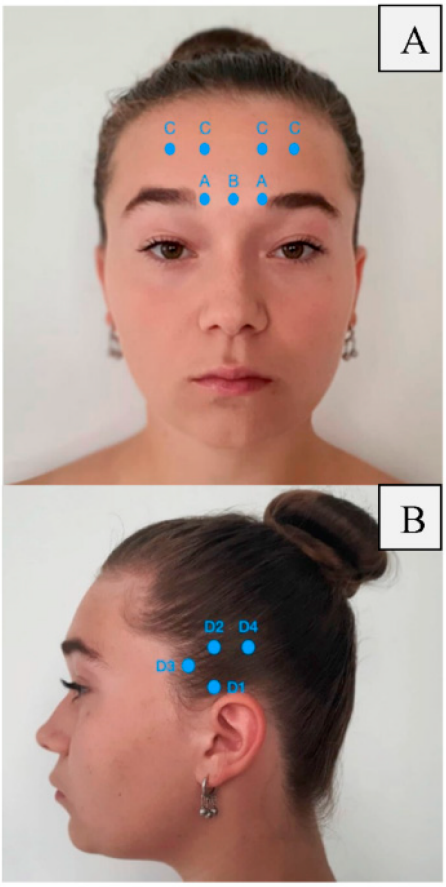
Over the years, several studies failed to indicate the positive effects of BoNT on episodic migraines [11][12]. For chronic migraines, the results were inconsistent. All patients responded to the treatment of botulinum toxin type A, but this response was not superior to the placebo [13][14].

A breakthrough in the use of ONA-BoNTA in the treatment of chronic migraine came in 2010. There were two studies: PREEMPT I and PREEMPT II (Phase III Research Evaluating Migraine Prophylaxis Therapy), in which a total of 1384 patients were enrolled [6][7]. In these two studies (PREEMPT I and II), all patients received a minimum intramuscular dose of 155 units of ONA-BoNTA administered to 31 injection sites across seven head and neck muscles using a fixed side. The minimum dose was 155 units, and the maximum dose was 195 units. The main results from the PREEMPT clinical program have established that ONA-BoNTA is a safe, well-tolerated and effective headache prophylactic treatment for CM [6][7][15]. PREEMPT results support previous studies, which identified chronic migraine patients as most likely to benefit from ONA-BoNTA treatment [13][14][16]. ONA-BoNTA dosing for CM by muscle using the PRREMPT injection program is shown in **Table 1**. When deciding on the dose and location of additional onabotulinumtoxin type A, the location of the patient's predominant pain and the severity is important.

Table 1. OnabotulinumtoxinA dosing in chronic migraine according to protocol PRREMPT [12].

Area of Injection	Recommended Dose
Frontalis	**20 units (4 sites)**
Corrugator	**10 units (2 sites)**
Procerus	**5 units (1 site)**
Occipitalis	**30 units (6 sites) + 10 units in 2 sites (follow the pain areas—optional injections)**
Temporalis	**40 units (8 sites) + 10 units in 2 sites (follow the pain areas—optional injections)**
Trapezius	**30 units (6 sites) + 20 units in 4 sites (follow the pain areas—optional injections)**
Cervical paraspinal muscle group	**20 units (4 sites)**
	Summary: 155–195 units

Retreatment with botulinum toxin occurs at 12-week intervals. Meanwhile, patients should keep a headache diary. It is recommended to repeat the injection every 12 months, at least three times. Moreover, the patient should receive additional injections in areas where, in particular, they have pain. This additional treatment strategy is called "Follow the pain", and it was also used by many of the PRREMPT testing sites before FDA approval. Injection points of the botulinum toxin are presented in **Figure 1**, **Figure 2** and **Figure 3**, where a patient with chronic migraine who was treated with botulinum toxin with a positive therapeutic effect is shown.



A

A. Corrugator (5 units each side)

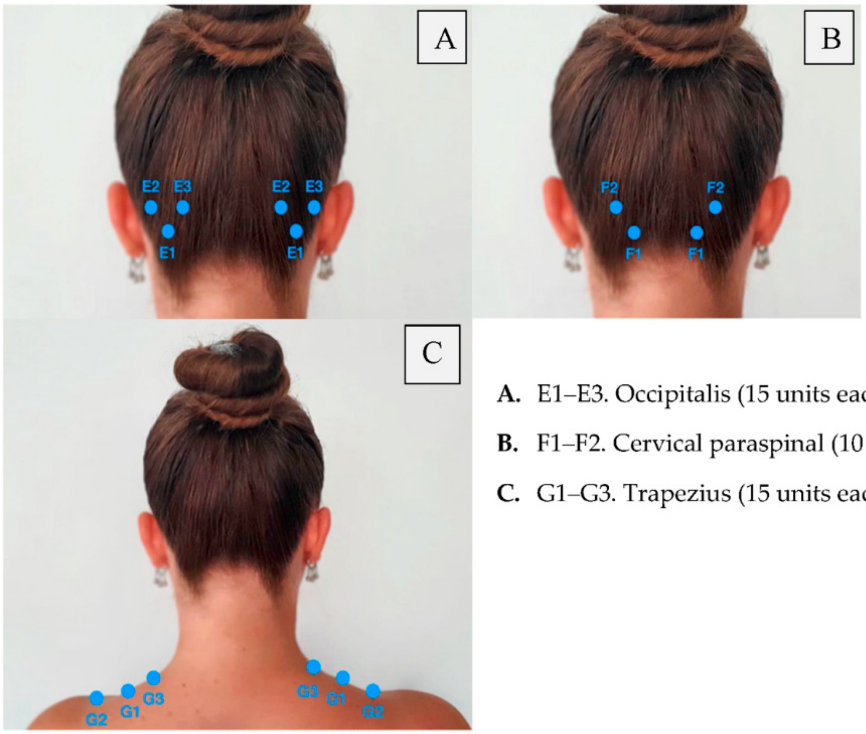
B. Procerus (5 units)

C. Frontalis (10 units each side)

B

D1–D4. Temporalis (20 units each side)

Figure 1. Frontalis and temporalis injections of botulinum toxin.



A. E1–E3. Occipitalis (15 units each side)

B. F1–F2. Cervical paraspinal (10 units each side)

C. G1–G3. Trapezius (15 units each side)

Figure 2. Posterior injections of botulinum toxin.

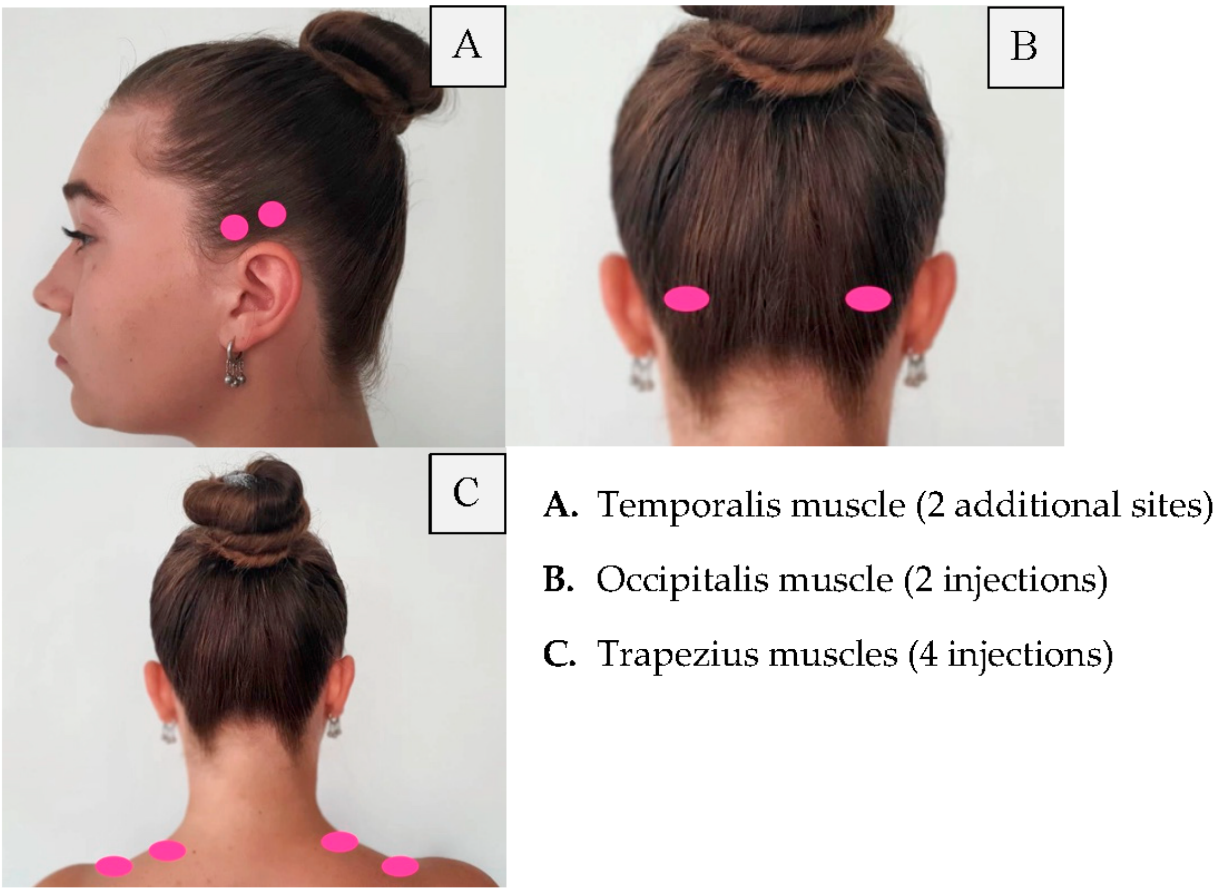


Figure 3. Follow the pain injection sites.

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