OnabotulinumtoxinA for Trigeminal Neuralgia Treatment

There is a growing body of evidence suggesting that onabotulinumtoxinA is a safe and effective treatment for trigeminal neuralgia.

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Trigeminal neuralgia (TN), as defined by the International Classification of Headache Disorders, 3rd edition, is a chronic and debilitating facial pain disorder that presents with recurrent paroxysms of sudden, severe, unilateral electric shock–like pain in the distribution of 1 or more divisions of the trigeminal nerve.[1] TN is a relatively rare condition, with an estimated annual incidence of 4.3 cases per 100,000 person-years in the US population. The repercussions of TN can have a profound effect on quality of life.[2] Individuals with TN often experience increased rates of psychiatric comorbidities, including depression, anxiety, and sleep disorders, compared with the general population.[3] The avoidance of innocuous pain triggers, such as brushing teeth, chewing, and swallowing, may result in an inability to maintain adequate oral hygiene, anorexia, weight loss, dehydration, and anxiety around performing these necessary activities. TN causes substantial disability, with up to 45% of individuals being absent from usual daily activities for 15 days or more in a 6-month period and more than 50% of individuals having severe anxiety and depression related to their pain disorder.[4,5]

Trigeminal Neuralgia Treatment

First-line pharmacologic treatment for TN typically includes anticonvulsant medications, such as carbamazepine, oxcarbazepine, lamotrigine, gabapentin, lacosamide, or the muscle relaxant baclofen. These drugs have poor tolerability, and side effects such as fatigue, cognitive impairment, dizziness, tremor, and electrolyte abnormalities are common, limiting their use. Rescue treatments for acute pain flares include infusion therapy and trigeminal nerve blocks. For individuals with classic TN, surgical procedures, such as microvascular decompression, gamma knife radiosurgery, and balloon compression, are available. Tolerability, long-term efficacy, and safety concerns arise with all the current treatment options.

OnabotulinumtoxinA for Trigeminal Neuralgia Treatment

OnabotulinumtoxinA, a Food and Drug Administration (FDA)–approved treatment for chronic migraine, has been used off-label by neurologists as a safe alternative for the management of TN. Several small studies have investigated the clinical efficacy and safety of onabotulinumtoninA, which have shown that it can be a safe and effective option in this population, especially in individuals who are unable to tolerate medications or are not candidates for neurosurgery.[6] In addition to reduction in pain intensity and attack frequency, there is also evidence supporting an increase in quality-of-life metrics after onabotulinumtoxinA injections for TN relative to placebo.[7]

Mechanism of Action

OnabotulinumtoxinA is a potent neurotoxic agent that has recently been shown to be effective in the treatment of neuropathic pain disorders. It targets a unique therapeutic pathway that differentiates it from conventional oral therapies in treating TN. The mechanism of action of onabotulinumtoxinA in mediating pain reduction is multifactorial. As an intramuscular injection, onabotulinumtoxinA is endocytosed at presynaptic nerve terminals and cleaves soluble N-ethylmaleimide-sensitive-factor attachment protein receptor (SNARE) proteins involved in

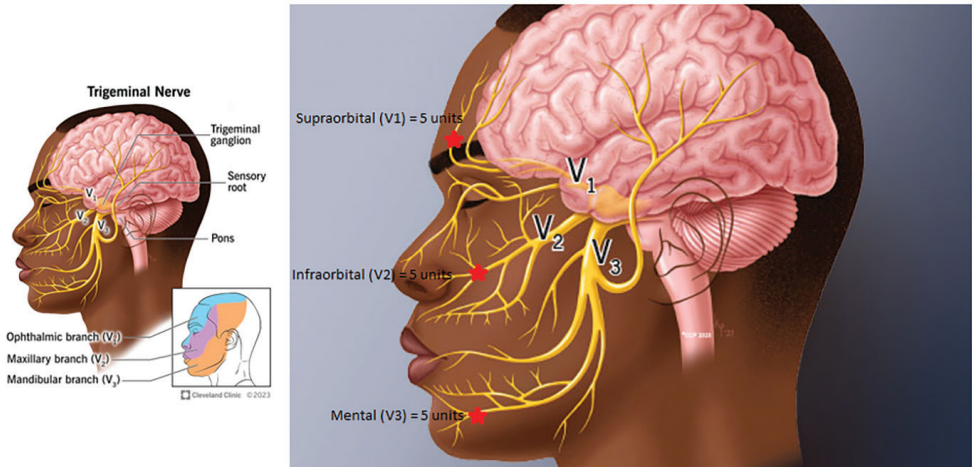

Figure. Trigeminal nerve branches and proposed injection sites. Adapted with permission from Cleveland Clinic. https://my.clevelandclinic.org/health/diseases/15671-trigeminal-neuralgia-tn. Updated 2021.

exocytosis, preventing the release of acetylcholine vesicles into the neuromuscular junction.[8] OnabotulinumtoxinA may also interfere with the release of other neurotransmitters involved in pain mediation, including substance P, calcitonin-related gene peptide, dopamine, norepinephrine, enkephalin, and neurokinin A.[9] By this effect, onabotulinumtoxinA decreases afferent nerve impulses to suppress neurogenic inflammation and prevent peripheral sensitization.

Effectiveness in Trigeminal Neuralgia

The effectiveness of onabotulinumtoxinA for TN was first discovered incidentally in 2002 when onabotulinumtoxinA was administered to an individual with both hemifacial spasm and TN, resulting in improvement in both twitching and pain.[10] Since then, several case series and randomized controlled trials (RCTs) have supported the use of onabotulinumtoxinA in individuals with medically refractory TN. A 2019 meta-analysis by Wei et al[11] reviewed the results of 4 RCTs on the use of onabotulinumtoxinA for TN and noted a significant improvement in reported pain values in comparison with placebo, with an estimated number needed to treat of 1.9 to achieve a 50% reduction in pain intensity. A more recent systematic review by Rubis and Juodzbalys[12] included 4 double-blind, placebo-controlled RCTs with 8- to 12-week follow-up. The mean visual analog scale score of the treatment group decreased by 68% (vs 21% in the placebo group), and the mean frequency of TN attacks decreased by 85% (vs 15% in the placebo group). There were no major adverse reactions reported, with the most common side effects being headache and facial asymmetry.[12]

An understanding of how this improvement in pain translates into meaningful changes in quality of life and mental health measures remains limited. The effect of onabotulinumtoxinA on quality of life in people with medically refractory TN has been explored in 1 retrospective review of 15 individuals.[9] Participants were administered a variable dose of onabotulinumtoxinA, ranging from 30 to 200 units. All participants reported large reductions in visual analog pain scale scores, decreasing from an average score of 9.3 at baseline to 3.7 by 2 weeks after the procedure, with stable pain reduction documented at 4 and 24 weeks after a single administration. Pain relief was so robust that 53% of the participants stopped taking carbamazepine or oxcarbazepine during the study period without relapse. Significant improvements were found in the physical and mental health domains of the Short Form–36 questionnaire on quality of life measures.

Treatment Protocol for Trigeminal Neuralgia

Because of the off-label nature of onabotulinumtoxinA treatment for TN, no standardization of injection sites exists. We propose a "follow-the-pain" protocol that is used by physicians at the Cleveland Clinic Headache Center. Individuals are counseled regarding the potential benefits of the procedure as well as the most common risks, which include facial muscle weakness, facial asymmetry, headache, and injection site reaction. Individuals are also informed that treatment success is considered a 50% improvement in pain severity and frequency. Clinicians must be aware of other potential risks and important prescribing information for onabotulinumtoxinA as noted on the drug label. Insurance approval for onabotulinumtoxinA 100 units administered every 3 months can be obtained for the Medicare-covered diagnosis of trigeminal nerve disorder (International Classification of Diseases, 10th revision code G50.8).[1]

Given the limited published data for onabotulinumtoxinA in the management of TN, it is not offered as a first-line treatment. Appropriate candidates for this treatment include people with classic TN pain in whom medications are ineffective or not tolerated, individuals with atypical features or with a diagnosis of trigeminal neuropathy, and individuals who are not deemed to be surgical candidates after review with the neurosurgical team.

In our practice, individuals are offered onabotulinumtoxinA therapy for TN for various indications, including

those with medically refractory pain; side effects limiting the use of oral pharmacologic agents; atypical features, including trigeminal neuropathies, postherpetic trigeminal nerve disorders, and burning mouth syndrome; and in individuals who are not ideal surgical candidates because of medical comorbidities or lack of true compression on neuroimaging.

Because no standardization of injection sites has been established, the injection protocol is decided upon following a discussion with the patient regarding the distribution of pain. Physicians inject onabotulinumtoxinA in the 3 branches of the trigeminal nerve (V1 [ophthalmic branch], V2 [maxillary branch], and V3 [mandibular branch]), depending on the location of the pain. We propose the following protocol:

- Five units injected at the supraorbital nerve (V1), infraorbital nerve (V2), and mental nerve (V3) (Figure); the opposite side is injected with the same number of units to maintain facial symmetry"follow-the-pain" injections in areas where the individual reports that pain exists (additional sites in V1, V2, V3, and temporalis): 2.5 to 5 units at each site
- Between 50 and 100 units used every 3 months, although individuals have benefited from lower doses

Dose adjustments can be made depending on clinical response or facial weakness.

Conclusion

There is a growing body of evidence suggesting that onabotulinumtoxinA is a safe and effective treatment for TN. We have seen positive results overall with this treatment at our tertiary care headache center. Clinicians should consider onabotulinumtoxinA treatment for individuals who have not responded to medications, are not candidates for surgery, or have atypical pain features. Further large-scale trials are needed to determine optimal dosing and injection protocols. ■

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