Botulinum Toxin for Trigeminal Neuralgia

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Key Points

- Trigeminal neuralgia (TGN) is a chronic painful condition, which compromises the quality of life of the patient
- Botulinum neurotoxin (BoNT) is an alternative to surgery in patients with drug-refractory TGN
- BoNT relieves symptoms and reduces drug requirement in patients with drug-refractory TGN
- BoNT can be useful in reducing drug-related adverse effects

Introduction

The American Academy of Neurology and the European Federation of Neurological Societies (AAN/EFNS) guidelines for the management of trigeminal neuralgia (TGN) suggest anticonvulsant medications as first line therapy; the surgical options utilized drug-refractory cases [1]. However, many patients are refractory to drugs, and surgical treatment may not be feasible owing to associated comorbid illnesses. Interventional procedures on the peripheral trigeminal nerve or on the Gasserian ganglion may not always be possible because of the unavailability of skilled

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practitioners. Botulinum neurotoxin (BoNT) is a promising mode of treatment, which can help such patients and provide pain relief.

Botulinum Toxin and Preparations

BoNT is produced by the anerobic bacteria Clostridium botulinum. The toxin has seven antigenic serotypes (A to G) and causes motor paralysis and botulism [2]. Out of the seven BoNTs, botulinum neurotoxin type-A is widely used for therapeutic purposes. Commonly available products include—onabotulinum toxin-A (Botox), incobotulinum toxin-A (Xeomin) and abobotulinum toxin-A (Dysport). Rimabotulinum toxin-B (Myobloc) is less commonly used. Botox and Xeomin are nearly equipotent with a conversion ratio of 1:1, and can be used interchangeably [3]. However, for Dysport, a ratio of 3:1 is used for conversion to Botox (3 units of Dysport = 1 unit of Botox) [4].

Mechanism of Action of BoNT

Botulinum toxin acts at the neuromuscular junction by inhibiting acetylcholine (Ach) release, thereby decreasing muscle fiber activity [5]. Specifically, BoNTs bind to various sites on the 'soluble *N*-ethylmaleimide-sensitive factor Attachment protein Receptor' (SNARE) proteins, which are essential for fusion of Ach vesicles to the plasma membrane and subsequent exocytosis of Ach into the neuromuscular junction [6]. However, nociceptive properties of the toxin are due to its effects on peripheral and central pain pathways. BoNT has been postulated to act through inhibition of various neurotransmitters, such as calcitonin gene related peptide (CGRP), substance P, glutamate, as well as the expression of transient receptor potential vanilloid 1 [7].

Role of BoNT in Pain Management

When first introduced, BoNT was primarily used to relieve symptoms in conditions with increased muscle tone or activity such as dystonia, strabismus and spasticity. In these conditions, the toxin inhibits the release of Ach, thereby decreasing neuromuscular transmission, and reducing muscle tone. Early studies found that in patients with painful cervical dystonia who were given BoNT injections, there was improvement of pain symptoms much earlier than dystonia-related features [8]. This led to a surge of studies investigating its effects in myriad painful conditions like myofascial pain, neuropathic pain syndromes, as well as other painful musculoskeletal conditions. In 2002, Michelo et al. [9] first reported significant relief of pain with BoNT in a patient with TGN. Subsequently, various reports have highlighted the efficacy of BoNT in alleviating pain attributed to TGN [10–12].

Safety and Efficacy

Clinical data on BoNT use is available in patients of different age groups. It is safe and equally effective across all ages. Even though some early animal studies have indicated reduction in fetal weight and decreased fetal ossification with BoNT use in pregnancy, there is only one published literature till date, that has reported spontaneous abortion in a pregnant patient who received BoNT [13]. Whether the abortion was clearly attributed to BoNT is not known. On the other hand, there are several case-reports of pregnant patients who have been treated with botulinum toxin without any adverse effects in the new-born [14, 15]. However, the drug continues to be labelled as risk-category C in pregnancy [13], and it is best to avoid using it in pregnant patients, unless newer recommendations for its use are amended. In any case of accidental injection in a pregnant lady, careful follow-up of the fetus is warranted. Similarly, BoNT is contraindicated in patients who have neuromuscular diseases.

Routes of Administration

BoNT is usually given as subcutaneous or submucosal injections at trigger points or areas representing most significant pain. The injection may be given as a fixed dose or calculated as per the area involved. In general, subcutaneous injection in the facial region is the commonest technique. However, there is always a risk of inadvertent intramuscular injections because facial muscles are very superficial. This may lead to temporary weakness or paralysis of facial muscles. There are some studies where the drug was deliberately given intramuscularly in the masseter or temporalis muscles, and have demonstrated better results compared submucosal injection [16, 17]. It is hypothesized that when injected intramuscularly, the toxin effectively travels in a retrograde direction through the axons of the motor branch of the trigeminal nerve due to its rich blood supply, leading to better efficacy compared to submucosal injections [17]. In one study, BoNT was directly injected into the maxillary and mandibular branches of the trigeminal nerve at the pterygopalatine fossa [12]. There is no common consensus for BoNT injections, with different routes, doses and duration-protocols followed by pain physicians, based on their personal experiences or institutional practices.

BoNT Use in TGN

There are four published randomized controlled trials (RCTs) examining the effect of BoNT in the treatment of TGN (Table 1) [16, 18–20]. A meta-analysis of these four RCTs, published in 2016 [21] found that the patients receiving BoNT had better response to treatment as well as lower frequency of paroxysms per day, as compared to placebo [21]. Various small, open-labelled trials studied use of BoNT in TGN. In a small study, injection of BoNT into maxillary and mandibular nerve roots was found be effective in providing 50% pain relief in 90% patients, and complete pain relief in 44% patients, at 6 months [12].

Table 1 Randomized trials in the treatment of TGN with BoNT

Study	Participants	Intervention	Outcome
Shehata et al. [19] Randomized single blinded placebo controlled	20 patients with TGN diagnosed according to IHS ICHD 2 criteria and less than 50% reduction in VAS or paroxysm frequency during the last 3 months with appropriate drugs	BoNT 5U (0.1 mL) or 0.9% saline (0.1 mL) in each trigger point, injection also into masseter muscle in mandibular branch involvement	Reduction in VAS at 12 weeks was by 6.5 in BoNT group and 0.3 for placebo. Significant decrease in the number of acute medications and an increase in quality of life
Wu et al. [18] Randomized, double blind, placebo controlled	42 patients with TGN diagnosed according to ICHD 2 criteria and failure of last treatment at baseline (pain intensity mean score 4; mean attack frequency 4 per day)	75U of BoNT-A (1.5 mL) or 1.5 mL of 0.9% saline	VAS scores and mean attack frequency at 12 weeks was significantly lower in the BoNT group compared to placebo. 68% patients in BoNT group responded with more than 50% reduction in VAS compared to only 15% patients in placebo
Zuniga et al. [16] Randomized double blind placebo controlled	36 patients with TGNs defined by Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms	50U of BoNT in 1 mL of 0.9% saline or 1 mL of 0.9% saline 10U in masseter muscle in V3 involvement	Three months after the injection, average VAS score of those treated with BoNT was 4.75 vs. 6.94 in those treated with placebo; *t* test $P = 0.01$)
Zhang et al. [20] Randomized double blind placebo controlled study	84 patients with TGN diagnosed according to ICHD II and >18 years), with failure of recent treatment (pain intensity mean score ≥4; mean attack frequency ≥4 per day; course >4 months)	1 mL of saline containing 50U of BoNT vs. 1 mL of plain saline injected in 20 points (0.05 mL/point)	3 months after the injection, statistically significant differences were observed in the average VAS score for subjects treated with BoNT compared to placebo

TGN Trigeminal neuralgia, *BoNT* Botulinum neurotoxin, *IHS* International Headache Society, *ICHD* International Classification of Headche Disorders, *VAS* Visual analog score

Author Experience and Institutional Protocol

The authors have an extensive experience of using BoNT in TGN. It has been believed that there is a significant reduction in the need for medications such as carbamazepine or gabapentin after BoNT treatment. Antiepileptic medications have a variety of unwanted effects and de-escalation of therapy helps in mitigating several of these adverse effects. In our Institute, patients are assessed for baseline pain intensity measured on the 11-point visual analogue scale (VAS, 0–10). BoNT-A is diluted (100 IU BOTOX, Allergan, USA in 2.5 mL normal saline), and intradermal or submucosal (if pain is over oral mucosa) injections are given using a tuberculin syringe with 30G needle. The injection sites are selected based on the patients'

narrative of most painful areas and specific trigger zones. Total painful area is calculated after demarcating it on the face. BoNT is injected in doses of 3 IU/cm^2 of pain surface area. None of our patient had suffered severe facial weakness using this protocol. Hence, it is believed to be a simple, safe and effective protocol which can be easily adopted elsewhere.

Conclusion

There is ample evidence to support of use of BoNT in TGN. This drug can drastically improve the quality of life and increase productivity of the individual by alleviating excruciating pain symptoms of TGN. Even though there is no comparative study of BoNT with neurosurgical decompression or other interventional modalities, it is a safe and effective modality of treatment. With careful explanation on potential side-effects, this treatment modality may be offered to all patients with drug-refractory symptoms, unless specific contraindications exist.

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