

A New Treatment Paradigm for Trigeminal Neuralgia using Botulinum Toxin Type A

Running Title: Treatment of Trigeminal Neuralgia using BoNT-A

Elizabeth Guardiani, MD¹

Babak Sadoughi, MD¹

Andrew Blitzer, MD, DDS¹

David Sirois, DMD, PhD²

1. New York Center for Voice and Swallowing Disorders, St. Luke's-Roosevelt Hospital,
New York, NY
2. New York University College of Dentistry, New York, NY

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Send Correspondence To:

Elizabeth Guardiani, MD
425 W. 59th St. 10th Floor
New York, NY 10019

O: 212-262-4444 F: 212-523-6364

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lizguardiani@gmail.com

Abstract:

Objectives: 1. To review the current data for the use of Botulinum toxin type A (BoNT-A) in trigeminal neuralgia (TN) 2. To describe the preferred injection technique of BoNT-A in TN 3. To propose a new treatment paradigm for TN incorporating the use BoNT-A

Data Sources: MEDLINE and Google Scholar databases

Review Methods: The current data on BoNT-A for trigeminal neuralgia were reviewed and analyzed for outcomes.

Results: 7 studies examining the use of BoNT-A were identified: 2 randomized double blind, placebo-controlled studies and 5 prospective case series. All studies found BoNT-A to be an effective treatment in the majority of patients and the results of the two randomized double-blind placebo-controlled study showed significant benefit over placebo. The majority of studies used an intradermal or subcutaneous injection technique. The most common side effect was transient facial paresis.

Conclusions: BoNT-A offers a safe, effective, local treatment for TN which is non-ablative in nature. BoNT-A should be considered in patients who have failed, become refractory to or are unable to tolerate first line pharmacologic treatments.

Key Words: Facial pain, Trigeminal Neuralgia, Botulinum toxin

Introduction:

Trigeminal neuralgia (TN) is a painful neuropathic condition involving cranial nerve V (CN V). It is characterized by paroxysmal episodes of intense, stabbing, electrical shock-like facial pain along the distribution of CN V, most commonly in the V2 or V3 division.¹ It is typically unilateral in nature, but some patients may experience pain at different times on both sides of the face. Often attacks are precipitated by even mild sensory stimulation of a so-called trigger zone in the affected area. TN may be caused by a blood vessel or small tumor pressing on the nerve, as well as by inflammatory causes of neuropathy such as multiple sclerosis, diabetes or Lyme disease.¹ When the cause of TN can clearly be identified, this is referred to as symptomatic TN. Often, the cause cannot be identified; this is referred to as essential or idiopathic TN. A newer classification system divides TN into Type 1 and Type 2 TN. Type 1 TN is characterized by intermittent sharp, lancinating, shock like pain with pain free intervals; Type 2 TN is characterized by constant pain and is more often associated with vascular compression.² First line treatment is typically with anticonvulsants, particularly carbamazepine. When pharmacotherapy is not effective or not tolerated, more invasive techniques such as microvascular decompression, stereotactic radiosurgery and percutaneous procedures on the trigeminal (Gasserian) ganglion can be effective. However, these procedures can also carry additional morbidity.

Botulinum Toxin Type A (BoNT-A) is a non-invasive therapy that has been demonstrated to be effective in a number of headache and pain conditions.³ In addition to its effect on the release of acetylcholine at the neuromuscular junction, BoNT-A has been found to inhibit the release of several pain-related neurotransmitters including substance P, calcitonin gene-related peptide and glutamate.⁴ These properties have led to the investigation of the use of BoNT-A in idiopathic trigeminal neuralgia.⁵⁻¹¹

Materials and Methods:

Literature Review

A review of the literature from 1989 (the year BoNT-A was introduced for cosmetic use) to 2013 on BoNT-A and TN was performed using a MEDLINE and Google Scholar search. The search terms included: Botulinum toxin, Botox, trigeminal neuralgia, tic douloureux and facial pain. Only original research, including abstracts, examining the use BoNT-A in humans with TN was included. All identified studies were in English. Studies examining chemically induced trigeminal pain, TN with associated facial spasm and case reports were excluded. All studies referencing one of the identified articles were reviewed using Google Scholar and the references of the identified studies were also manually searched to identify any other pertinent articles. Included in this review is a randomized, double blind, placebo-controlled crossover previously performed by the two senior authors in this study (AB, DS), published in abstract form only (Sirois, et al).⁵

Injection Technique

Prior to injection, a grid of the facial pain (including any mucosal surfaces) is created in conjunction with the patient. The grid is determined by a mapped area drawn by the physician related to the patient's perception of hyperesthesia and allodynia (Figure 1A). The hyperesthesia is mapped with touch of cotton and allodynia with pinprick. The larger area is used for the mapping and grid lines are placed one centimeter apart. BoNT-A is then injected intradermally at each cross-hatch (Figure 1B). Our preferred starting dose is 2.5u of BoNT-A in 0.1cc saline/cm². If the patient does not note significant benefit (>50% global pain reduction) after 4 weeks, a booster dose of 2.5u/cm² may be given. If no response is noted after a booster dose, the patient is considered a non-responder to treatment. If the patient does respond to a booster dose, 5u/cm² can be used on subsequent treatments. These doses are based on the study performed by the two senior authors.⁵ Facial paresis is an expected complication of this treatment, especially when higher doses are used. We often give patients contralateral BoNT-A to achieve facial symmetry.

Results

A total of seven studies examining the use of BoNT-A in TN were identified, two randomized double blind placebo-controlled trial (including the one performed by the two senior authors) and five case series.⁵⁻¹¹ All of the patients in the studies reviewed had been tried on medical therapy without relief prior to being enrolled in the study. Primary study outcomes examined were similar between studies and included: % global pain reduction, number of attacks and visual analog scale (VAS) scores. Technique and dosing varied from study to study. All of the studies reviewed found BoNT-A treatment to be effective in the majority of the patients treated.⁵⁻¹¹ The

two randomized double blind studies (Sirois et al, Wu et al) showed statistically significant improvement in patients treated with BoNT-A over placebo (defined as >50% global pain reduction). In study performed by the two senior authors, there was also a significant improvement in quality of life in patients treated with BoNT-A vs. placebo. A summary of the studies and their results of these studies can be found in Table I.

Discussion

The mechanism by which BoNT-A affects pain conditions has become better understood in recent years. In animal models, BoNT-A has been found to inhibit the release of the pain-related neurotransmitters, calcitonin gene-related peptide (CGRP) and substance P, within cultured sensory ganglions.^{12, 13} In addition, Aoki found that rats pretreated with subcutaneous BoNT-A had a significantly reduced formalin-evoked glutamate release in the hind paw.⁴ By directly inhibiting the release of peripheral neurotransmitters, BoNT-A is thought to be able to directly inhibit peripheral sensitization and indirectly inhibit central sensitization.⁴ Human studies have shown benefit in conditions such as chronic neuropathic pain¹⁴, migraine headaches¹⁵ and temporomandibular myofascial pain¹⁶. In addition, pretreatment with subcutaneous BoNT-A has been shown to reduce capsaicin-induced trigeminal pain and vasomotor reactions when compared with placebo in humans.¹⁷

This review highlights the mounting body of evidence for the use of BoNT-A in the treatment of trigeminal neuralgia. The majority of the studies use a subcutaneous or intradermal injection technique. We believe intradermal injections in the area of facial allodynia to be the method of choice given the location of unmyelinated sensory nerve endings within the papillary dermis.¹⁸.

. The literature review suggests subcutaneous injections are also effective, likely due to their proximity to the papillary dermis. Turk, et al. used a different technique and administered a large bolus of toxin above and below the zygomatic arch, presumably trying to target the injection at the Gasserian ganglion. This technique seems less logical given that BoNT-A is thought not to transverse the myelin sheath, however they did show some improvement in their non-controlled study. Transient facial asymmetry was noted in all studies which used subcutaneous or intradermal injections. This is an expected side effect given the proximity to the superficial facial musculature and the known effect of BoNT-A at the neuromuscular junction. However, because of the obvious facial asymmetry in some patients, keeping the double blind during a study can be problematic. If the facial asymmetry is of cosmetic concern, patients can be given contralateral toxin to achieve facial symmetry. The duration of benefit for BoNT-A varies by study, the majority show benefit for at least 3 months, with some studies (Bohuli, et al and Turk, et al) showing benefit up to six months. In general, BoNT-A was well tolerated across the studies and appears to offer a safe and effective treatment for refractory trigeminal neuralgia.

The current guidelines by American Academy of Neurology and the European Federation of Neurological Societies (AAN-EFNS) recommend carbamazepine or oxcarbazepine as first line treatment for trigeminal neuralgia and that drugs such as baclofen, lamotrigine, and pimozone may also be considered.¹⁹ They recommend the use of routine imaging in the workup of patients with TN to evaluate for the presence of a tumor or vascular malformation. They go on to state that in patients who are refractory to medical therapy, early surgical therapy, such as percutaneous procedures on the Gasserian ganglion, stereotactic radiosurgery and microvascular

decompression, may be considered. However, these procedures are not without risk and may carry additional morbidity. Percutaneous procedures result in facial hypoesthesia in almost half of the patients treated and a small amount of patients may develop facial dysesthesia or anesthesia dolorosa, which can be permanent and more troublesome than the original disease. Stereotactic radiosurgery also carries the risk of facial hypoesthesia or paresthesia, albeit less than percutaneous procedures.¹⁹ Microvascular decompression is used only in those patients in whom vascular compression is suspected and carries along with it the risk of posterior fossa surgery which may include CSF leak, hematoma, and infarct in up to 4% of patients and aseptic meningitis in up to 11%.¹⁹ BoNT-A offers a novel, local, reversible treatment alternative that is non-ablative and provides significant pain relief without permanent side effects and without the risk of multiple drug interactions. We propose a new treatment paradigm for TN incorporating the use of BoNT-A (Figure 2).

Conclusions:

BoNT-A offers a safe and effective treatment for TN and should be considered in patients who have failed, become refractory to or are unable to tolerate oral medications prior to an ablative procedure.

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Figure 1A: Mapping of facial pain for injection

Figure 1B: Schematic diagram for injection

Figure 2: Proposed treatment algorithm for TN incorporating BoNT-A



Figure 1A: Mapping of facial pain for injection
274x246mm (180 x 180 DPI)

Accel

Table I. Summary of Current Evidence for the Use of BoNT-A in TN. RDBPC=Randomized, double-blind, placebo controlled, *=statistically significant result

Study	Type of Study	#patients	Technique used	Outcomes	Complications
Wu CJ, et al. 2012 ⁶	RDBPC trial	40 (21 BoNT-A, 19 placebo)	75 u at 15 pts (5u/point), given between the epidermis and the dermis or submucosal	68% response rate (defined as $\geq 50\%$ improvement of symptoms) vs. 11% in placebo *	Facial asymmetry (5pts) Transient edema (3pts)
Bohluli, et al. 2011 ⁷	Prospective Case series	15	50 u total at trigger points	All patients had improvement in global assessment scale, # and intensity of attacks*	Transient paresis of buccal branch in 3 pts.
Zuniga, et al. 2008 ⁸	Prospective Case series	12	20-50u subcutaneously at trigger points/painful areas	10/12 patients improved ($>50\%$ reduction in VAS & #attacks)	Transient facial asymmetry in 1 patient
Piovesan, et al. 2005 ⁹	Prospective Case series	13	Grid of painful area created, average 3.22u/cm given subcutaneously	All patients had improvement in VAS scores*	Transient facial asymmetry in 3 pts, ptosis in 1 pt
Borodic, Acquadro 2002 ¹⁰	Prospective Case series	11 TN pts (44 total pts in study)	Subcutaneous injections in affected dermatome 1cm apart, 30-50u total	8/11 patients had $\geq 50\%$ reduction in pain intensity/frequency	Transient facial asymmetry in 29 pts (only 5pts found troublesome)
Turk, et al. 2005 ¹¹	Prospective Case series	8	100u injected in 2 50u boluses immediately above and below zygomatic arch (1.5-2cm depth)	Decreased VAS scores and # attacks for the total series*	Transient dysesthesia in 1 pt, transient trouble chewing in 1 pt
Sirois, et al. 2011 ⁵	RDBPC trial	17 (8 placebo,	Grid of painful area created,	11/15 had $\geq 50\%$ global pain relief	1 patient had transient

		15 BoNT-A after placebo crossover)	2.5u/cm ² given intradermally, booster dose of 2.5u/cm ² given to non-responders at 4 weeks.	after BoNT-A compared to 2/8 placebo *. Improved quality of life in responders to treatment.	troublesome lip droop, 1/3 pts had mild facial asymmetry
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