The Laryngoscope

Systematic Review

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

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Objectives: To review the current data for the use of Botulinum toxin type A (BoNT-A) in trigeminal neuralgia (TN) and to describe the preferred injection technique of BoNT-A in TN. 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 TN were reviewed and analyzed for outcomes.

Results: Seven studies examining the use of BoNT-A were identified: Two randomized double-blind, placebo-controlled studies and five 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 that is nonablative 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.

Level of Evidence: N/A

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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. 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 is 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 noninvasive 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 TN.[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

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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 only in abstract form (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 (Fig. 1A). The hyperesthesia is mapped with a touch of cotton and allodynia with a pinprick. The larger area is used for the mapping and grid lines are placed 1 cm apart. BoNT-A is then injected intradermally at each cross-hatch (Fig. 1B). Our preferred starting dose is 2.5 units of BoNT-A in 0.1 cc saline/cm^2. If the patient does not note significant benefit (>50% global pain reduction) after 4 weeks, a booster dose of 2.5 units/cm^2 may be given. If no response is noted after a booster dose, the patient is considered a nonresponder to treatment. If the patient does respond to a booster dose, 5 units/cm^2 can be used on subsequent treatments. These doses are based on the study performed by the two senior authors (AB, DS).[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 [AB, DS]) 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[5,6] showed statistically significant improvement in patients treated with BoNT-A over placebo (defined as >50% global pain reduction). In the study performed by the two senior authors (AB, DS)[5] there was also a significant improvement in quality of life in patients treated with BoNT-A versus placebo. A summary of the studies and the 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

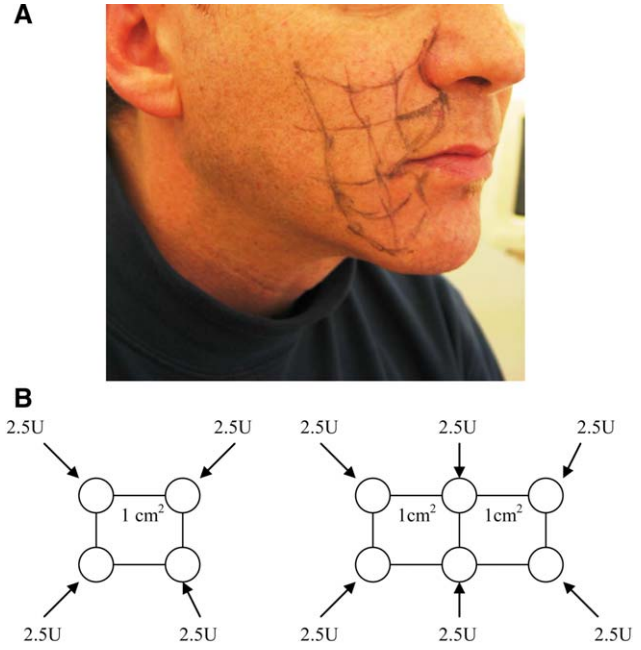

Fig. 1. **A**. Mapping of facial pain for injection. **B**. Schematic diagram for injection. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

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 pain,[14] migraine headaches[15] and temporomandibular myofascial pain.[16] In additional, 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 TN. 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 that subcutaneous injections are also effective, likely due to their proximity to the papillary dermis. Turk et al.[11] 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 noncontrolled study. Transient facial asymmetry was noted in all studies that 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

TABLE I.
Summary of Current Evidence for the Use of BoNT-A in Trigeminal Neuralgia.

Study	Type of Study	No. Patients	Technique Used	Outcomes	Complications
Wu CJ, et al. 2012[6]	RDBPC trial	40 (21 BoNT-A, 19 placebo)	75 units at 15 points (5 units / point), given between the epidermis and dermis or submucosally	68% response rate (defined as $\geq$50% improvement of symptoms) vs. 15% in placebo*	Facial asymmetry in 5 patients; transient edema in 3 patients
Bohluli, et al. 2011[7]	Prospective case series	15	50 units total at trigger points	All patients had improvement in global assessment scale,* no. attacks, and VAS scores.*	Transient paresis of buccal branch in 3 patients
Zuniga, et al. 2008[8]	Prospective case series	12	20–50 units subcutaneously at trigger points/painful areas	10/12 patients improved ($>$ 50% reduction in VAS and no. attacks)	Transient facial asymmetry in 1 patient
Piovesan, et al. 2005[9]	Prospective case series	13	Grid of painful area created, average 3.22 units /cm^2 given subcutaneously	All patients had improvement in VAS scores.*	Transient facial asymmetry in 3 patients; ptosis in 1 patient
Borodic, Acquadro 2002[10]	Prospective case series	11 TN pts (44 total patients in study)	Subcutaneous injections in affected dermatome 1 cm apart, 30–50 units total	8/11 patients had $\geq$50% reduction in pain intensity/ frequency.	Transient facial asymmetry in 29 patients (only 5 patients found troublesome)
Turk, et al. 2005[11]	Prospective case series	8	100 units injected in 2 50 unit boluses immediately above and below zygomatic arch (1.5–2 cm depth)	Decreased VAS scores and no. attacks for the total series*	Transient dysesthesia in 1 patient; transient trouble chewing in 1 patient
Sirois, et al. 2011[5]	RDBPC trial	17 (8 placebo, 15 BoNT-A after placebo crossover)	Grid of painful area created, 2.5 units /cm^2 given intradermally; additional 2.5 units /cm^2 given to nonresponders at 4 weeks	11/15 had $\geq$50% global pain relief after BoNT-A compared to 2/8 placebo.* Improved quality of life in responders to treatment	Transient troublesome lip droop in 1 patient; mild facial asymmetry in 1/3 patients.

*= statistically significant result.
RDBPC = randomized, double-blind, placebo controlled.

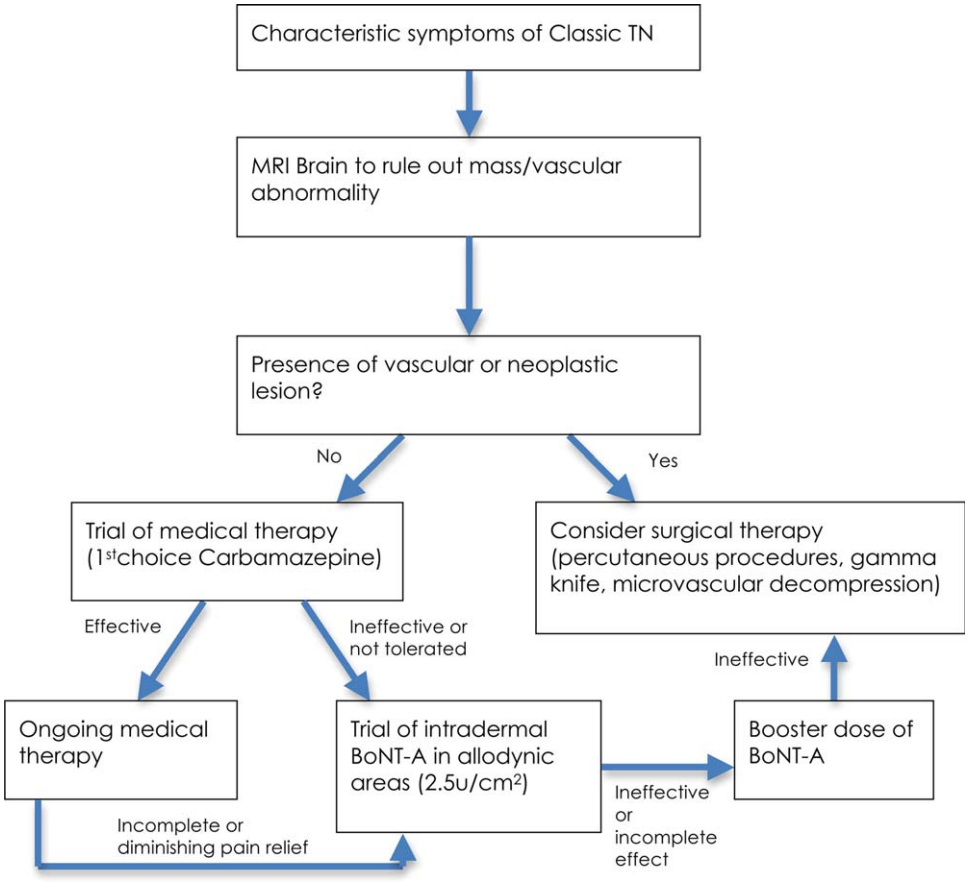

Fig. 2. Proposed treatment algorithm for trigeminal neuralgia incorporating BoNT-A. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.].

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 (Bohluli et al. and Turk et al.[11]) showing benefit up to 6 months. In general, BoNT-A was well tolerated across the studies and appears to offer a safe and effective treatment for refractory TN.

The current guidelines by American Academy of Neurology and the European Federation of Neurological Societies (AAN-EFNS) recommend carbamazepine or oxcarbamazepine as first-line treatment for TN; drugs such as baclofen, lamotrigine, and pimozide 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. In addition, 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 nonablative 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 (Fig. 2).

CONCLUSION

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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