Intraoral Administration of Botulinum Toxin for Continuous Dentoalveolar Neuropathic Pain: A Case Series

Isabel Moreno-Hay, DDS, PhD

Pratishtha Mishra, BDS, MS

Jeffrey P. Okeson, DMD

Orofacial Pain Center
College of Dentistry
University of Kentucky
Lexington, Kentucky, USA

Correspondence to:
Dr Isabel Moreno-Hay
740 S Limestone, Room E214
Kentucky Clinic
Lexington, KY 40536, USA
Fax: 859.323.0001
Email: imo226@uky.edu

Submitted July 20, 2017;
accepted September 19, 2018.

Aims: To examine the analgesic effect, safety, and tolerability of intraoral administration of onabotulinum toxin A (BoNT/A) in patients suffering from intractable continuous dentoalveolar neuropathic pain. **Methods:** Eight patients (six women and two men) of ages ranging from 21 to 73 years (mean [standard deviation] 52.4 [16.1] years) suffering from continuous dentoalveolar pain for a mean duration of 5.8 (4.4) years received a submucosal injection of 10 to 25 units of BoNT/A into the vestibular mucosa surrounding the painful site. Pain intensity levels were recorded using a verbal rating scale (VRS). Safety and tolerability of BoNT/A were measured based on patient self-report, including any adverse effects reported by the patient at the injection site. **Results:** Five of eight patients reported positive pain reduction. In this group, mean pain intensity on a 0–10 VAS was 4.8 (2.2) at baseline and 2.6 (2.1) at postinjection. The analgesic effect was maximal between 7 and 14 days postinjection and lasted for 1 to 8 weeks before subsequently returning to the pre-injection levels. No adverse effects were reported at the injection sites. One patient noted transient partial hemifacial paralysis. **Conclusion:** These results suggest the potential therapeutic benefit of BoNT/A in the management of continuous dentoalveolar neuropathic pain. Further investigations conducted via well-controlled studies in the area of orofacial pain are warranted. *J Oral Facial Pain Headache 2019;33:160–164. doi: 10.11607/ofph.2031*

Keywords: *chronic pain, continuous neuropathic pain, dentoalveolar neuropathic pain, onabotulinum toxin A, orofacial pain*

Botulinum toxin (BoNT) is a potent neurotoxin produced by the bacteria *Clostridium botulinum* and other *Clostridium* species. The mechanism by which the toxin blocks the release of acetylcholine at the neuromuscular junction from the presynaptic efferent (motor) nerve endings has been widely studied. More recently, BoNT has also been reported to have an effect on afferent (sensory) neurons by inhibiting the release of various neurotransmitters and neuropeptides. This appears to be independent of its action on muscle tone and secretory glands at the periphery. There are seven different serotypes of neurotoxin (A–G) identified. Serotype A is the most commonly used in the clinical setting since it was first purified in the mid 20th century.[1]

In animal models, onabotulinum type A (BoNT/A) has been shown to have an effect on the accumulation of presynaptic calcitonin gene-related peptide (CGRP) of afferent neurons inhibiting the peptide exocytosis, thus potentially alleviating pain.[2] This antinociceptive mechanism was first described after peripheral[3] and intrathecal[4] administration of BoNT/A in formalin-induced inflammatory pain models, suggesting a modulatory effect on pain sensitization processes. In a capsaicin inflammatory pain model, BoNT/A infiltration previous to induction of the inflammation prevented mechanical and thermal hyperalgesia.[5] Additionally, in neuropathic pain models, the administration of peripheral and intrathecal BoNT/A reduced mechanical and thermal hyperalgesia.[6–10] These data suggest that BoNT/A reduces central sensitization regardless of the route of administration.

Table 1 Demographic Data (n = 8)

Case	Gender	Age (y)	Dentoalveolar pain location	Duration (y)	Trauma	Sensory changes
1	F	53	Left maxillary third molar	4	–	Allodynia
2	F	66	Right maxillary premolar/lateral incisor	2	–	–
3	M	73	Left mandibular lateral incisor	15	Dental treatment, #23	Allodynia
4	F	63	Maxillary central incisors	7	Dental treatment, #9	Allodynia
5	F	21	Mandibular central incisors	2	Orthognathic surgery	Allodynia
6	F	49	Right mandibular premolar/first molar	9	Extraction, #30	Allodynia
7	F	43	Left mandibular second premolar/molar	7	–	Allodynia
8	M	51	Left mandibular canine/incisors	1	–	Allodynia

It is noteworthy that part of the effect of BoNT has also been observed distant to the site of injection. Hence, it has been hypothesized that the neurotoxin can be retrogradely transported through neuronal axons.[11]

Since the first case series published in 2004,[12] several human studies have demonstrated the analgesic benefit of BoNT/A in the management of different conditions, such as chronic tension type headaches[13] and chronic neck pain.[14] More recently, the PREEMPT study concluded that BoNT/A could be used as a preventive therapy in chronic migraine patients[15]; thus, FDA approval was obtained.

For neuropathic pain conditions, the revised systematic review and meta-analysis funded by the Special Interest Group on Neuropathic Pain (NeuPSIG) concluded that BoNT/A should be recommended as a third line of treatment, particularly in neuropathic pain conditions with a presumed local pain generator (eg, posttraumatic painful neuropathies).[16] Notwithstanding that the quality of the evidence is limited since only six RCTs were available, subcutaneous administration of 50 to 200 units to the painful area has been recommended every 3 months. Minimal side effects were reported.

Neuropathic pain is defined according to the International Association for the Study of Pain (IASP) as "pain caused by a lesion or disease of the somatosensory nervous system."[17] It can be classified based on temporal features (ie, episodic or continuous).[18,19] Continuous dentoalveolar neuropathic pain has been traditionally described as atypical odontalgia or phantom toothache and has also been described in the literature as persistent dentoalveolar pain.[20] In 2013, the International Headache Society (IHS) proposed the term painful traumatic trigeminal neuropathy (PTTN) to describe pain felt in the trigeminal distribution associated with sensory disturbances and related to a traumatic event.[21]

To the best of the authors' knowledge, there are no clinical trials published investigating the effect of intraoral administration of BoNT/A in continuous dentoalveolar neuropathic pain. The aim of this case series was to examine the analgesic effect of a single intraoral injection of BoNT/A in patients suffering from continuous dentoalveolar pain.

Materials and Methods

Institutional Review Board approval was obtained for this retrospective consecutive case series, which was conducted at the Orofacial Pain Center at the College of Dentistry of the University of Kentucky between August 2015 and January 2017.

Patients

A total of eight patients diagnosed with continuous dentoalveolar neuropathic pain at the Orofacial Pain Center received a single intraoral injection of BoNT/A as a coadjutant therapy to their pharmacologic treatment (Table 1). Each patient presented with continuous pain felt in the dentoalveolar tissues with no clinical or radiographic evidence of dental and/or periodontal pathology. Six patients were women and two were men, and their ages ranged from 21 to 73 years (mean [standard deviation (SD)] 52.4 [16.1] years). The mean (SD) duration of pain was 5.8 (4.7) years. In 50% of the cases, an invasive dental or surgical procedure was related to the onset of pain. The remaining 50% did not report any precipitating event, although two of these patients recieved dental treatment in an attempt to treat the pain, which in one case increased the initial level of pain (Table 1, case 7). Positive sensory changes such as allodynia were noted in the affected area, except for in case 2. In six patients, temporary pain reduction was obtained after application of benzocaine gel 20% to the affected area. Intra- and extraoral examinations were otherwise negative.

All of the patients included had been managed with various combinations of medications depending on the patient's response. The medications included anticonvulsants such as gabapentin with dosages ranging from 900 mg to 2,700 mg; pregabalin 75 mg up to 300 mg; oxcarbazepine 300 mg to 600 mg; antidepressants such as duloxetine 30 mg to 120 mg; and amitriptyline 10 to 20 mg. One patient was under a narcotic contract for methadone, 80 mg per day, to manage the pain. In spite of the polypharmacotherapy, the mean (SD) average pain reported prior to treatment using a 0–10 verbal rating scale (VRS; 0 = no pain, 10 = extreme pain) was 4.75 (1.7) at baseline.

Table 2 Results in Pain Reduction Levels After Intraoral Administration of BoNT/A

Case	BoNT/A (units)	VRS baseline	VRS result	Onset (d postinjection)	Duration (wk postinjection)	Tolerance	Side effects
1	20	4	4	–	–	Good	–
2	25	2	1	12	1	Good	–
3	20	4	1	7	5	Good	–
4	10	5	2	12	6	Good	–
5	20	4	4	–	–	Painful	–
6	10	6	6	–	–	Good	–
7	10	5	3	14	8	Good	–
8	10	8	6	15	5	Good	Facial muscle weakness

VRS = verbal rating scale.

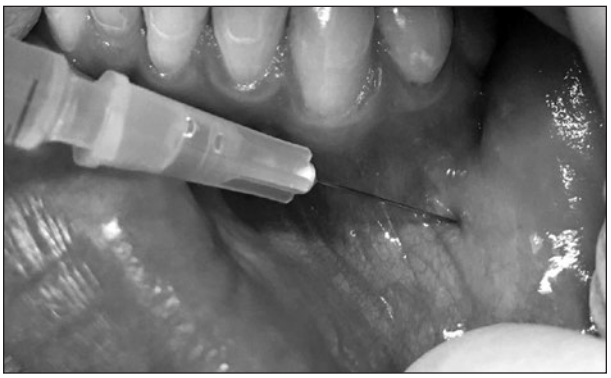

Fig 1 Intraoral administration of BoNT/A injected into the vestibular mucosa over the painful area.

Methods

Onabotulinumtoxin A (BOTOX) was obtained from Allergan, New Jersey, USA; 100 units of BoNT/A were reconstituted in 4 mL of 0.9% sterile sodium chloride (NaCl) solution at concentrations of 25 units per 1 mL. After written consent was obtained, each subject received between 10 and 25 units of BoNT/A infiltrated to the painful area. Injections were performed in the vestibular mucosa or attached gingiva with a 30-gauge 1-inch needle at 2- to 4-mm depth (Fig 1), and doses were divided among three evenly distributed sites (Table 2).

Tolerance of the procedure and secondary side effects were recorded on the basis of patient report. Patients were requested to contact the clinic by phone and report the onset of postinjection pain reduction (if pain reduction occurred) and the duration of the therapeutic benefit. Pain intensity was recorded by means of a VRS. Patients were followed over a period of 3 months after the procedure.

Results

Five of the eight patients reported pain relief after the intraoral BoNT/A injection. The mean (SD) pain intensity at baseline for these five patients was 4.8 (2.2) on a VRS, and at postinjection it was 2.6 (2.1). Pain reduction of > 50% was achieved in three patients (cases 2, 3, and 4); the other two patients had 25% and 40% pain relief, respectively (Table 2). The mean average reduction in pain intensity was 50%.

The maximal initial analgesic effect was felt between 7 and 14 days postinjection (mean [SD] analgesic onset of 12 [3.1] days). The duration of the therapeutic benefit lasted between 1 and 8 weeks (mean duration 5 [2.5] weeks) before subsequently returning to the pre-injection levels. In two of the patients who achieved more than 50% pain reduction, the therapeutic effect lasted for 5 weeks (Table 2, cases 3 and 4).

Overall, the procedure was well tolerated and no complications were reported, except for one patient who reported that the injection was painful. No adverse effects were reported at the injection sites. At the 3-month follow-up, one patient reported transient difficulty smiling after the injection that lasted for a few weeks (Table 2). Four of the eight patients reported significant improvement in quality of life and expressed their interest in having the procedure repeated in the future.

Discussion

In this case series, intraoral submucosal injection of BoNT/A was effective in providing an analgesic effect in five out of eight patients suffering from continuous dentoalveolar neuropathic pain. Patients tolerated the procedure well, with no complications noted at the intraoral injection site and minimal side effects reported at the 3-month follow-up interview. These findings are similar to results published in previous case reports in which the intraoral approach was used to administer BoNT/A for the management of continuous dentoalveolar neuropathic pain.[22,23]

Interestingly, significant reduction in pain intensity has been reported in all studies despite the fact that dosages have varied considerably: with a dosage of 15 to 30 units the analgesic effect lasted 2

to 4 months[23]; up to 100 units, the analgesic effect was reported to last 2 months.[22] In the present study, more than 50% pain reduction was achieved in three patients with small amounts of BoNT/A ranging from 10 to 25 units, and the therapeutic benefit reported by the patients lasted up to 2 months with a dosage of 20 units. Furthermore, failure of the treatment was not related to the use of the lowest dosages, as two of the nonresponders received 20 units.

These observations are in accordance with the findings reported in a recent literature review on the use of BoNT/A for the management of orofacial neuropathic pain conditions, including trigeminal neuralgia.[24] According to these authors, 25 to 50 units divided into multiple injections could be proposed for the intraoral administration of BoNT/A in neuropathic pain conditions. However, further studies are needed to corroborate this proposed dosage.

In the present study, all patients that achieved some pain reduction after the BoNT/A injection noted that eventually the pain returned to the baseline intensity level. As mentioned previously, the longest therapeutic benefit was achieved in one case with a maximum of 8 weeks of pain reduction. Four of the five responders to the BoNT/A expressed interest in repeating the procedure.

As acknowledged in a recent randomized clinical trial,[25] repeated injections of BoNT/A improved the therapeutic effect in peripheral neuropathic pain conditions. Moreover, the authors observed that a quarter of the initial nonresponders reported therapeutic benefit from the second administration despite the lack of improvement after the first. Thus, the authors concluded that repeated administrations might be necessary to determine whether a patient responds to BoNT/A. Therefore, further investigations are needed to evaluate the potential benefit of periodic infiltrations in patients suffering from continuous dentoalveolar pain.

Moreover, among the eight patients recruited for this case series with a diagnosis of continuous neuropathic pain, only 50% reported a previous traumatic event related to the onset of pain. Two cases received root canal treatment, one case a dental extraction, and one underwent orthognathic surgery. According to IHS,[21] the latter cases meet the criteria for PTTN, whereas the other 50% reported pain with an unknown precipitating factor. One case received dental treatment for her pain condition resulting in an aggravation of her symptoms. It is not uncommon that by the time patients are diagnosed with continuous dentoalveolar pain they have already received some type of dental treatment.[26] According to these findings, the presence of a traumatic event did not seem to predict the patient's response to the treatment, nor did gender or duration of pain.

Taking into consideration the small sample size, these findings do not support the hypothesis that treatment outcomes for neuropathic pain conditions could be predicted depending on their clinical features, as proposed previously in the literature.[25] Furthermore, in this patient population the presence of allodynia did not predict the response to treatment, nor did the response to the application of 20% benzocaine gel. Two of the three nonresponders obtained significant pain relief with the topical application of local anesthetic. In the responder group, four out of five patients responded favorably to the benzocaine gel.

However, these results should be interpreted with caution due to the limitations of this study. The small size of the sample recruited and the lack of a control group do not allow a dose-response assessment nor a statistical analysis of the data obtained to be performed.

Conclusions

The intraoral submucosal injection of BoNT/A to the painful area of continuous dentoalveolar neuropathic pain resulted in a decrease of pain intensity in more than 50% of patients. The minimum pain reduction achieved was at least a 25% decrease from baseline. Pain reduction of > 50% was achieved in three patients, and in two of them the therapeutic benefit lasted for 5 weeks. Despite the limitations of a case series, these findings suggest that BoNT/A may have an analgesic effect in patients suffering from continuous dentoalveolar pain. Additionally, the treatment was well tolerated. However, further studies are warranted with well-controlled designs to determine the appropriate dosage of BoNT/A and to evaluate the benefits and safety of repeated injections.

Acknowledgments

The authors report no conflicts of interest.

References

1. Pavone F, Luvisetto S. Botulinum neurotoxin for pain management: Insights from animal models. Toxins (Basel) 2010;2:2890–2913.
2. Dolly JO, O'Connell MA. Neurotherapeutics to inhibit exocytosis from sensory neurons for the control of chronic pain. Curr Opin Pharmacol 2012;12:100–108.
3. Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain 2004;107:125–133.

4. Luvisetto S, Marinelli S, Lucchetti F, et al. Botulinum neurotoxins and formalin-induced pain: Central vs. peripheral effects in mice. Brain Res 2006;1082:124–131.
5. Bach-Rojecky L, Lacković Z. Antinociceptive effect of botulinum toxin type a in rat model of carrageenan and capsaicin induced pain. Croat Med J 2005;46:201–208.
6. Marinelli S, Luvisetto S, Cobianchi S, et al. Botulinum neurotoxin type A counteracts neuropathic pain and facilitates functional recovery after peripheral nerve injury in animal models. Neuroscience 2010;171:316–328.
7. Bach-Rojecky L, Relja M, Lacković Z. Botulinum toxin type A in experimental neuropathic pain. J Neural Transm (Vienna) 2005;112:215–219.
8. Park HJ, Lee Y, Lee J, Park C, Moon DE. The effects of botulinum toxin A on mechanical and cold allodynia in a rat model of neuropathic pain. Can J Anaesth 2006;53:470–477.
9. Bach-Rojecky L, Salković-Petrisić M, Lacković Z. Botulinum toxin type A reduces pain supersensitivity in experimental diabetic neuropathy: Bilateral effect after unilateral injection. Eur J Pharmacol 2010;633:10–14.
10. Filipović B, Bach-Rojecky L, Lacković Z. Lasting reduction of postsurgical hyperalgesia after single injection of botulinum toxin type A in rat. Fundam Clin Pharmacol 2010;24:43–45.
11. Antonucci F, Rossi C, Gianfranceschi L, Rossetto O, Caleo M. Long-distance retrograde effects of botulinum neurotoxin A. J Neurosci 2008;28:3689–3696.
12. Klein AW. The therapeutic potential of botulinum toxin. Dermatol Surg 2004;30:452–455.
13. Relja M, Telarović S. Botulinum toxin in tension-type headache. J Neurol 2004;251(suppl 1):112–114.
14. Miller D, Richardson D, Eisa M, Bajwa RJ, Jabbari B. Botulinum neurotoxin-A for treatment of refractory neck pain: A randomized, double-blind study. Pain Med 2009;10:1012–1017.
15. Dodick DW, Turkel CC, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: Pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache 2010;50:921–936.
16. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. Lancet Neurol 2015;14:162–173.
17. International Association for the Study of Pain (IASP). IASP Terminology. IASP, 2017. http://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698&navItemNumber=576. Accessed 16 November, 2018.
18. Okeson JP. Bell's Oral and Facial Pain, ed 7. Chicago: Quintessence, 2014.
19. De Leeuw R. Orofacial Pain: Guidelines for Assessment, Diagnosis, and Management, ed 5. Chicago: Quintessence, 2013.
20. Nixdorf DR, Drangsholt MT, Ettlin DA, et al. Classifying orofacial pains: A new proposal of taxonomy based on ontology. J Oral Rehabil 2012;39:161–169.
21. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33:629–808.
22. Herrero Babiloni A, Kapos FP, Nixdorf DR. Intraoral administration of botulinum toxin for trigeminal neuropathic pain. Oral Surg Oral Med Oral Pathol Oral Radiol 2016;121:e148–e153.
23. Cuadrado ML, García-Moreno H, Arias JA, Pareja JA. Botulinum neurotoxin type-A for the treatment of atypical odontalgia. Pain Med 2016;17:1717–1721.
24. Moreau N, Dieb W, Descroix V, Svensson P, Ernberg M, Boucher Y. Topical review: Potential use of botulinum toxin in the management of painful posttraumatic trigeminal neuropathy. J Oral Facial Pain Headache 2017;31:7–18.
25. Attal N, de Andrade DC, Adam F, et al. Safety and efficacy of repeated injections of botulinum toxin A in peripheral neuropathic pain (BOTNEP): A randomised, double-blind, placebo-controlled trial. Lancet Neurol 2016;15:555–565.
26. Baad-Hansen L, Benoliel R. Neuropathic orofacial pain: Facts and fiction. Cephalalgia 2017;37:670–679.