Botulinum toxin A for management of refractory concurrent buccal and inferior alveolar nerve post-traumatic neuropathies: a case report

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Abstract
Painful post-traumatic trigeminal neuropathy (PPTTN) can result from iatrogenic injury to one or more branches of the trigeminal nerve during oral surgical procedures such as tooth extractions. Like other chronic neuropathic pain conditions, PPTTN can significantly alter the patient’s quality of life, especially when pharmacological treatment is ineffective or not tolerated. As such, new treatment options have been investigated, including local injections of botulinum toxin type A (BTX-A). A 29-year-old woman presented to our tertiary orofacial pain clinic for evaluation of chronic electric shock-like pain attacks and severe allodynia in the territory of the right inferior alveolar nerve and buccal nerve following right mandibular third molar extraction 3 years prior. Following several failed attempts at classic pharmacological management (including carbamazepine, venlafaxine, duloxetine, pregabalin, clonazepam, and amitriptyline), BTX-A injections were administered in the vicinity of the right mental nerve. This treatment provided significant improvement in the patient’s condition and overall quality of life with no significant adverse effects. Because both neuropathies were significantly improved by remote BTX-A injections, this case report provides preliminary clinical evidence supporting spinopetal transport of BTX-A, as shown in animal models, as an underlying pathophysiological mechanism of BTX-A-mediated analgesia.
Introduction

Painful post-traumatic trigeminal neuropathy (PPTTN) is defined as “unilateral or bilateral facial or oral pain following and caused by trauma to the trigeminal nerve(s), with other symptoms and/or clinical signs of trigeminal nerve dysfunction.”1 PPTTN is a complication of many oral surgical procedures, including dental extractions, after which it occurs in 0.5% to 12.0% of cases.2 Like other chronic neuropathic pain conditions, PPTTN can significantly alter the patient’s quality of life,3–5 especially when improperly diagnosed and/or managed.

The pain experienced by patients with PPTTN is typically described as a continuous burning sensation that is sometimes associated with short-lasting paroxysms, which may occur both spontaneously and following mechanical stimulation of the skin and/or mucosa in the area of innervation of the injured nerve(s).6 Pain onset is variable, occurring either immediately following nerve injury or up to 3 to 6 months following trauma.1,6 The pain is classically associated with sensory dysfunction, either positive (hyperalgesia, allodynia, itching) or negative (hypoesthesia, anesthesia).

Current management of PPTTN commonly relies on pharmacological and/or surgical treatment.2,6 As for other neuropathic pain conditions, pharmacological treatment is based mainly on antiepileptic drugs (carbamazepine, oxcarbazepine, pregabalin, gabapentin) and/or tricyclic antidepressants (amitriptyline, nortriptyline), although no formal guidelines exist for this specific condition. Unfortunately, the analgesic effect of such drugs is often limited or hampered by significant adverse effects and/or contraindications.2 Surgical treatment is controversial and can be offered as a second-line option in specific cases only. Indeed, many patients who have undergone peripheral surgical interventions have experienced worsening pain.2

Considering the quite challenging management of PPTTN, new therapeutic options have emerged with the hope of obtaining an analgesic effect that is better tolerated by patients. One such therapeutic option is local injections of botulinum toxin type A (BTX-A). There is growing evidence that BTX-A may have a significant analgesic effect in both traumatic7–9 and non-traumatic painful neuropathies10–13 with few adverse effects.10,14 More specifically, there is growing evidence that BTX-A may be effective in painful post-traumatic trigeminal neuropathy,15,16 as discussed in a recent review by Moreau et al.17 From a pathophysiological standpoint, it has been suggested that BTX-A is endocytosed in local peripheral afferents, where the protease activity of BTX-A cleaves Soluble N-ethylmaleimide-sensitive factor Attachment protein REceptor (SNARE) complexes, thus inhibiting vesicular fusion and subsequent neurotransmitter release.17 Animal studies have shown evidence of spinopetal transport of BTX-A along the primary afferent into the dorsal root ganglia.
and/or the central terminal, where it can
block second afferent activation.\textsuperscript{18,19} To
the best of our knowledge, however, no
such spinopetal transport has been evi-
denced in humans to date.

We herein present a case involving a
young woman who presented with refracto-
ry concurrent PPTTN of the right inferior
alveolar nerve and buccal nerve following
extraction of her right mandibular third
molar 3 years prior. The PPTTN in this
case was successfully managed by BTX-A
injections in the vicinity of the right
mental nerve. Therapeutic and pathophysi-
ological implications of the present case are
also discussed in this report.

Case report

The reporting of this study conforms to the
CARE guidelines.\textsuperscript{20}

A 29-year-old woman with no medical
history presented to our tertiary orofacial
pain clinic in January 2020 for chronic
intractable spontaneous and evoked pain
in the right labiomental and preauricular
regions following bilateral mandibular
third molar extractions under general anes-
thesia in another hospital in 2017. The
patient reported significant complications
following the surgery, notably pain-related
speech impairment for the first 5 postoper-
ative days, major facial and labial postop-
erative edema, and trismus lasting for
1 month.

When the initial pain subsided, the
patient developed complete right labio-
mental anesthesia followed several weeks later
by paresthesias and finally unbearable pain
in the innervation territories of the right
inferior alveolar nerve and buccal nerve.
The pain persisted despite numerous treat-
ments and medical consultations in several
hospitals and private practices.

At the time of the patient’s initial consul-
tation in our clinic 3 years later, she
reported continuous dull “crushing” pain
accompanied by “electric shock”–like pain
upon light touch to the right labiomental
region. Chewing, talking, and brushing her
teeth would also elicit such painful parox-
ysms, as did vibrations applied to the lower
half of her face. Everyday activities were
strongly hampered by such painful activities
as talking, touching her lips, eating, kissing,
sleeping on her right side, and wearing a
mask (quite troublesome in the time of
COVID-19-related mandatory mask-
wearing). Because her professional activity
(hospital nutritionist) required frequent
talking, thus eliciting significant painful
paroxysms, she had been placed on disabil-
ity leave by her general practitioner a few
weeks prior and was working part-time
only at the time of her visit to our clinic.

Physical examination revealed significant
right labiomental mechanical (static) and
thermal (cold and hot) allodynia accompa-
nied by an avoidance response when the
patient was approached. Right masseter
muscle palpation was painful, but not left
palpation; the pain was limited to the site of
palpation, which was suggestive of reactive
myospasm (i.e., local myalgia as defined in
the diagnostic criteria for temporomandib-
ular disorders\textsuperscript{21}). Intraoral examination
revealed significant mechanical static (not
dynamic) allodynia in the innervation territ-
ory of the right buccal nerve (Figure 1). No
temporal summation of pain was objecti-
fied. Considering the obvious allodynia in
both sites, no further sensory testing was
deemed necessary. No mucosal lesion,
unhealed socket, or neuroma was found
along the right mandibular body and/or
branch.

A three-dimensional cone-beam comput-
ed tomography (CBCT) imaging study had
been performed 1 month after the third
molar surgery (in 2017). This imaging
examination showed perforation of the lin-
gual mandibular cortex of the right lower
third molar socket in the immediate vicinity
of the inferior alveolar nerve bundle, the
shape of which was consistent with a burr-induced iatrogenic injury (Figure 2). Brain magnetic resonance imaging had also been performed around the same period, but no significant anomalies were revealed. No further imaging studies were deemed necessary.

The patient’s history, physical examination findings, and CBCT results were consistent with a diagnosis of PPTTN of the right inferior alveolar nerve and buccal nerve based on the criteria established by Benoliel et al.\(^6\) and the International Classification of Headache Disorders, 3rd edition (ICHD-3 13.1.2.3).\(^1\) More specifically, the PPTTN affecting the inferior alveolar nerve fulfilled the five criteria described by Benoliel et al.\(^6\) (definite neuropathic pain), whereas the PPTTN affecting the buccal nerve fulfilled only four criteria (probable neuropathic pain) because of a lack of imaging evidence. Both neuropathies could also be classified as “chronic neuropathic pain after peripheral nerve injury” according to the International Classification of Diseases, 11th revision (ICD-11).\(^22\) From a mechanistic standpoint, the PPTTN affecting the inferior alveolar nerve was thought to be the result of iatrogenic burr-induced nerve dilaceration, whereas the buccal nerve had possibly been injured during the third molar flap incision (nerve transection) and/or

**Figure 1.** Clinical view of the territory of intraoral buccal mucosa allodynia, mapped using a dermographic marker pen. This territory of allodynia was compatible with the innervation territory of the buccal nerve (see Reference 23 for comparison).

**Figure 2.** Postoperative coronal (left) and sagittal (right) cone-beam computed tomography images of the socket of the right mandibular third molar 1 month after extraction. Note the burr-shaped lingual cortex destruction (arrows) in the immediate vicinity of the inferior alveolar nerve bundle (circle), suggestive of iatrogenic injury.
reflection (nerve stretching), both frequent causes of buccal nerve injury.\textsuperscript{23,24} The patient had consulted several physicians during the few years after the extraction, and multiple pharmacological treatments were instituted either alone or in combination: carbamazepine, venlafaxine, duloxetine, clonazepam, pregabalin, and amitriptyline. All treatments were given at sufficient doses over several months (for each treatment) but with unsatisfactory results: the patient experienced either insufficient analgesic effects or too many adverse effects such as weight gain, difficulty focusing, memory loss, and fatigue. Right mental nerve block with a long-lasting anesthetic (ropivacaine at 7.5 mg/mL) suppressed the evoked labiometal pain but not the spontaneous pain. Therefore, at 3 years post-injury, the patient’s painful neuropathic condition was considered refractory according to the criteria by Smith et al.\textsuperscript{25} and new therapeutic options were sought.

Local injections of BTX-A in the vicinity of the mental nerve were considered. The expected risks and benefits of such experimental treatment were presented to the patient, who eagerly accepted because of the significant alteration in her overall quality of life and morale. Informed verbal and written consent to undergo treatment was obtained before the first injection. At that time, the patient was still taking clonazepam at 2.5 mg/mL (6 drops three times daily) and pregabalin (150 mg daily), which provided minimal but noticeable pain relief. We decided not to modify this analgesic regimen for the time being.

Because the patient raised significant concern regarding possible speech impairment secondary to labial paralysis following the BTX-A injection, we opted for a progressive two-step injection technique. An initial dose of 25 IU of BTX-A (50 IU in 1 mL saline, Botox\textsuperscript{®}; Allergan, Dublin, Ireland) was injected in the vicinity of the right mental foramen at the level of the interproximal region between the first and second premolars at a 2-cm depth from the marginal gingiva (Figure 3). This location was based on the CBCT imaging results (Figure 4). The injection was performed using a 1-mL syringe (BD Plastipak; Becton, Dickinson and Company, Franklin Lakes, NJ, USA) and a 30-G hypodermic needle (Hypodermic Needle Pro, 30G × 1/2”, 0.3 × 13 mm; Smiths Medical, Minneapolis, MN, USA). The BTX-A dose was chosen to obtain a rapid and significant analgesic effect, whereas a small injection volume (0.5 mL) was sought to limit possible diffusion into the surrounding muscles (especially those in the lower labial region). Following injection, discomfort and flushing appeared immediately but subsided rapidly. A follow-up appointment was set for day 15, and the patient was instructed to keep a detailed pain diary every day until the appointment.

At the 15-day follow-up, the patient reported a progressive 25% improvement in spontaneous and mechanically evoked pain.
pain but persistence of thermal allodynia (Figure 5), which had appeared between days 5 and 10 following the injection. The lower lip allodynia, but not the chin allodynia, had disappeared. The intraoral buccal mucosa allodynia had also completely disappeared. No facial asymmetry was observed at rest. Labial paresis was minimal and did not impact speech or food intake (Video 1). The patient sought a second
injection, duly informed of the possibility of increased labial paresis, but was clearly enthused by the preliminary analgesic results.

A second injection was performed using the same dose (25 IU) and volume (0.5 mL) but with a more distoapical injection point to ensure infiltration of the posteroinferior aspect of the mental nerve bundle (which innervates the chin region), as schematically illustrated in Figure 6. A further decrease in pain intensity was noted (63% decrease compared with baseline pain), and the chin allodynia completely disappeared (Figure 5). Spontaneous pain persisted but with a lower and tolerable intensity. The labial paresis was slightly aggravated, but still without any significant effect on speech or facial esthetics (Video 2).

The overall therapeutic efficacy was evaluated based on three parameters: pain intensity (via an 11-point numerical rating scale), anxiodepressive comorbidities (via the Hospital Anxiety and Depression questionnaire), and overall impression of change (via the Patient Global Impression of Change questionnaire). The efficacy of the BTX-A injection therapy is summarized in Table 1. Overall, significant improvement was observed in all parameters based on the classic 30% improvement cutoff relevant to the pain field. Significant improvement in the patient’s overall mood was also reported, as was observed by both our team and the patient’s husband.

At the 3-month follow-up, the pain had progressively returned to its initial stage (i.e., to the level reported during the first consultation in our clinic), and the patient sought another injection. A repeat injection was performed at that time with similar efficacy (decrease in the numerical rating scale score from 8 to 4). At the 6-month follow-up, upon learning of the patient’s pregnancy, the injections were stopped for safety reasons with plans to resume them after the pregnancy.

Discussion

BTX-A is one of seven types of antigenically different exotoxins produced by the gram-positive anaerobic bacteria *Clostridium botulinum*, which is known for its powerful paralytic effect (the main complication of botulism), and has been exploited for medical use in the fields of neuromuscular disease and cosmetology. On a molecular level, BTX-A is a polypeptide composed of a 100-kDa heavy chain linked to a 50-kDa light chain by a disulfide bridge. The heavy chain binds to neurons, allowing the light chain to be translocated and exert its enzymatic protease activity. Upon endocytosis, the light chain cleaves the SNARE complexes. This prevents vesicular exocytosis of numerous neurotransmitters and neuromodulators, including acetylcholine, the main neurotransmitter responsible for muscle contraction at the neuromuscular junction level.

Apart from the paralytic effect of BTX-A, recent evidence has suggested an analgesic effect resulting from blockade of the release of algogenic neuropeptides (such as
substance P, neurokinin A, and calcitonin gene-related peptide), but also of glutamate, in small-diameter type C primary afferent nerve fibers. This blockade prevents neurogenic inflammation and nociceptive signaling.

The analgesic effect of BTX-A is thought to take place not only in the peripheral terminal but also in the dorsal root ganglion and central terminal following spinopetal (axonal retrograde) transport as evidenced in preclinical models. Although several clinical studies have supported the analgesic effect of BTX-A in neuropathic pain and particularly in painful post-traumatic trigeminal neuropathy (as noted in a review by Moreau et al.), there is still much to learn regarding the underlying pathophysiology and efficacy of BTX-A in routine pain management.

The present report describes the successful management of two post-traumatic neuropathies affecting two branches of the same nerve (buccal nerve and inferior alveolar nerve) by perineural injections of BTX-A in the vicinity of the mental nerve, a terminal branch of the inferior alveolar nerve. This observation is consistent with the retrograde axonal transport of BTX-A shown in animal models but, to the best of our knowledge, never before evidenced in the clinical setting. The anti-allodynic and analgesic effects observed in this case may have thus resulted from the uptake of BTX-A in the mental nerve and subsequent spinopetal transport to the trigeminal ganglion and/or the trigeminal nucleus via the inferior alveolar nerve. Notably, because rare mental–buccal nerve anastomoses have been reported, spinopetal transport could also have occurred in the buccal nerve, although this is less probable in the present case (considering the well-defined and limited innervation territory of the right buccal nerve as shown in Figure 1 and the resolution of the buccal allodynia following the first injection into the anterior aspect of the mental nerve, devoid of such anastomoses). To the best of our knowledge, such a perineural injection technique in the vicinity of the mental nerve has not been reported in the literature to date, especially in the treatment of an iatrogenic third molar extraction-related trigeminal nerve injury.

From a clinical standpoint, it is interesting to note that BTX-A provided significant pain relief in a patient with 3-year refractory painful neuropathy. This further supports its use in neuropathic pain management either alone or as an add-on therapy, in adherence with the most recent neuropathic pain management guidelines.

Nevertheless, it is possible that BTX-A does not exert an analgesic effect on all peripheral neuropathies depending on the neuropathic pain phenotype. Further studies involving specific neuropathic pain phenotype clustering could help to clarify this important issue.

From a technical standpoint, considering the remote effect of BTX-A, perineural mental nerve injections may prove to be

| Table 1. Assessment of analgesic efficacy of BTX-A. |
|-----------------------------------------------|
| Before BTX-A injections | After BTX-A injections |
|----------------------------|----------------------|
| **Numerical rating scale score** | | |
| IAN = 8/10 | IAN = 3/10 |
| Buccal nerve = 7/10 | Buccal nerve = 0/10 |
| **Hospital Anxiety and Depression score** | | |
| Anxiety = 8/21 | Anxiety = 7/21 |
| Depression = 10/21 | Depression = 8/21 |
| **Patient Global Impression of Change score** | | |
| N/A | 40% improvement |

BTX-A, botulinum toxin A; IAN, inferior alveolar nerve; N/A, not applicable.
very practical in the treatment of more proximal inferior alveolar nerve injuries resulting from commonly performed surgical interventions such as mandibular third molar extraction (as in the present case) or sagittal split mandibular osteotomy, with limited functional impairment (lip paresis) as evidenced herein (Videos 1 and 2). Nevertheless, such injections also have a limited risk of significant adverse effects related to the paralytic effect of BTX-A. Indeed, in all of the published cases in which intraoral injections of BTX-A were performed to treat trigeminal neuropathic pain, the injections were administered in the vicinity of the initial injury where the pain was felt by the patient. However, this would not have been possible in the present case because of the proximal location of the injuries and associated risks of dysphagia and/or hypoglossal nerve palsy that could have arisen from the spread of the toxin. Multiple injections of small doses and small volumes of BTX-A in the vicinity of the mental nerve seem to provide sufficient impregnation of the nerve’s branches without significant spread of the toxin that would lead to lip muscle paralysis.

Several inherent limitations apply to the present case, the findings of which should be analyzed with caution. This case report presents the successful symptomatic management of a single patient with no data regarding potential long-term treatment (painful post-traumatic trigeminal neuropathy is often chronic, if not incurable) and with a possible confounding placebo effect. However, we believe that a possible placebo effect is of minimal relevance in the present case, considering the timing of the analgesic effect (consistent with the onset of BTX-A pharmacological activity) and the severity/chronicity of the patient’s illness. Concurrent pharmacological treatments (clonazepam and pregabalin) could have also confounded the analysis of the analgesic effect of BTX-A; however, these medications were maintained at the same dosage during BTX-A treatment and had been taken at a stable dosage for many months before the first BTX-A injection. Finally, recall bias is always possible when comparing post-treatment pain with pre-treatment pain. Such bias was hopefully mitigated by the use of a pain diary, which required daily analysis of the patient’s pain levels during the onset of the pharmacological effect of BTX-A.

**Conclusion**

The present report describes the symptomatic management of two chronic refractory painful post-traumatic trigeminal neuropathies resulting from concurrent iatrogenic injuries to the buccal nerve and inferior alveolar nerve following mandibular third molar extraction. This symptomatic management involved perineural mental nerve BTX-A injections, bringing further support to the small volume of previously gathered scientific evidence.

A significant analgesic effect on both spontaneous and evoked pain was observed, with limited treatment-related functional impairment (minor lip paresis with no visible facial asymmetry or speech impairment). Further studies using the same injection protocol will be required to fully assess its efficacy and safety. BTX-A injections in the vicinity of the mental nerve are a potentially effective and safe treatment option for the symptomatic management of painful post-traumatic trigeminal neuropathy, even in cases involving multiple trigeminal branches and/or chronic refractory cases. Additional patient cohorts will be required to confirm this preliminary evidence.

**Ethics statement**

No review board approval was requested for the publication of the present case report (according to French bylaw, no ethics board approval is
required to publish a single case report as long as patient consent is obtained, as occurred in the present case). All identifying information was removed from the case presentation. The patient provided written consent for treatment and publication of this case report.

Data availability
Data pertaining to the present case report can be obtained, following anonymization, upon reasonable request to the corresponding author.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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