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CASE REPORT

Onabotulinum toxin a treatment for posttraumatic trigeminal neuropathic pain: case series and literature review

Huann Lan Tan[1,2], Pankaew Yakkaphan[1,3], Amandine Beke[1], Tara Renton[1,*]

[1]Faculty of Dentistry, Oral & Craniofacial Science, King's College London, SE5 8AF London, UK
[2]Faculty of Dentistry, The National University of Malaysia, 50300 Kuala Lumpur, Malaysia
[3]Faculty of Dentistry, Prince of Songkla University, 90112 Songkhla, Thailand

***Correspondence**
tara.renton@kcl.ac.uk
(Tara Renton)

Abstract

This case series aimed to assess the treatment outcomes of onabotulinum toxin A (BTX-A) in patients with refractory posttraumatic trigeminal neuropathic pain (PTNP) and to conduct a narrative review of the evidence for BTX-A in PTNP. Thirteen patients were treated with BTX-A infiltrations. Patient demographic and pain characteristics, BTX-A administration, and treatment outcomes were retrospectively analyzed. Papers retrieved after a literature search of articles on PTNP treatment using BTX-A were reviewed. Six patients reported an improvement in pain 3 months after the initial BTX-A injection, with 4 patients reporting a 50% reduction. Two patients achieved an 80% reduction in pain score over 3 years of BTX-A therapy. Three patients reported temporary ipsilateral facial muscle weakness. The literature review revealed five case reports on the use of BTX-A in PTNP patients that reported similar effectiveness to the present cohort study. BTX-A may be a potential treatment modality for refractory PTNP, thus reducing the need for polypharmacy. Multiple intraoral BTX-A injections administered over the painful sites are well tolerated, safe and easily practiced. High-quality studies are required to evaluate the long-term therapeutic efficacy and side effects of BTX-A therapy.

Keywords

Botulinum toxin; Neuropathic pain; Submucosal; Traumatic trigeminal neuropathy; Trigeminal neuropathy

1. Background

Posttraumatic neuropathy is limited to a patient whose sensory neuropathy has been caused by mechanical, chemical or thermal trauma. The International Classification of Orofacial Pain (ICOP) [1] has defined posttraumatic neuropathy as a neuropathic site that coincides with the anatomical area where the trauma occurred followed by neuropathy development within 6 months and associated somatosensory changes. Positive neuropathic signs include burning, sharp or shooting pain, allodynia (mechanical or thermal), hyperalgesia, and hyperpathia [1], in accordance with the International Classification of Headache Disorders (ICHD-3) [2]. Finnerup *et al.* [3] have further summarized and revised the grading system of the International Association for the Study of Pain (IASP) Special Interest Group on Neuropathic Pain (NeuPSIG) [4] on the level of certainty in diagnosing possible, probable and definite neuropathic pain. These diagnostic criteria are extended to the trigeminal nervous system, emphasizing the need for clinical neurosensory evaluation.

With the increasing demand for dental treatment, trigeminal nerve injuries related to dentistry are increasing. Common causes of orofacial nerve injuries are local anesthesia (direct needle trauma), endodontic treatment, tooth extraction, and dental implant surgery. All surgical procedures carry a risk of sensory nerve injury [5]. With an estimated 2 million mandibular third molar extractions undertaken in the United Kingdom per year [6], several reviews have highlighted the prevention and management of posttraumatic peripheral trigeminal neuropathic pain (PTNP) related to dental surgery [7, 8]. A proportion of 70% of nerve injury patients [9] will develop chronic PTNP, commonly reported within [10, 11] and outside the trigeminal system [12, 13]. PTNP may not be life-threatening, but the iatrogenic pain added to the traumatic incidence [14, 15] could cause a remarkable impact on a patient's quality of life [14–16]. It is suggested that orofacial trigeminal pain has a higher affective component impact on psychosocial function than other regional pain [15]. Chronic PTNP in the orofacial region also impedes essential daily functions, including the patient's speech, mastication and swallowing [11].

Various task forces have published international guidelines on managing patients with neuropathic pain, such as the National Institute for Health and Care Excellence, UK (NICE), the European Federation of Neurological Societies, the German Society of Neurology, and the American Academy of Pain Medicine. These task forces suggest the importance of mul-

tidisciplinary treatment, including psychologic and pharmacologic adjunct therapy such as neurostimulation and, rarely, surgical intervention [17–21]. The NICE guidelines also detail the importance of the nonspecialist's role in pharmacologic management of neuropathic pain in adults [21]. The primary recommendations for treating patients with neuropathic pain are systemic and topical drugs using mainly tricyclic antidepressants and gabapentinoids, but their side effects result in poor patient compliance [22–24]. Thus, pharmacotherapy is often ineffective for managing patients with PTNP, and other strategies are needed [9].

Recent articles have demonstrated the effectiveness of botulinum toxin in managing neuropathic pain [17, 25, 26]. The therapeutic analgesic value of intradermal or subcutaneous administration of onabotulinum toxin A (BTX-A) has been demonstrated in trigeminal neuralgia [27–29], postherpetic neuralgia [30, 31], posttraumatic neuralgia [27, 32], postsurgical neuralgia [33, 34], and diabetic neuropathy [35, 36] disorders. In addition, BTX-A is relatively safe, with reversible effects, and is a recommended adjunct therapy for headaches [37] and migraines [38–40]. Published case reports on using BTX-A for treating intraoral neuropathic pain have been promising, as patients exhibited considerable improvement in pain and quality of life [41, 42]. However, there is limited evidence regarding BTX-A as an alternative treatment for intraoral PTNP. The present article attempts to retrospectively analyze 13 PTNP patients treated with BTX-A and to review the literature on the use of BTX-A in PTNP.

2. Literature review

Electronic literature searches of MEDLINE (PubMed) and Google Scholar were performed using the following keywords: botulinum toxin; traumatic trigeminal neuropathy; neuropathic pain; trigeminal neuropathy; and post-traumatic neuropathy. Articles in the English language that described the causation events for trauma or injuries prior to PTNP and the use of BTX-A were included in the literature review.

The literature search revealed three case reports and two case series [42–46]. The clinical characteristics of patients and their treatment modalities are summarized in Table 1. All included patients received first-line pharmacology treatment but responded poorly to it, except for in Yoon *et al.* [43], who reported a 60% decrease in dysesthesia but failure to achieve continuous pain-free episodes following 6 months of pharmacotherapy. The primary cause of trigeminal maxillary or mandibular nerve branch injuries was dental treatments or dental exodontia, implant, endodontic or orthognathic surgery. No serious adverse effects following BTX-A injection were reported in four studies [42, 44–46], but patients did experience sensory changes such as allodynia and hyperalgesia. Although the dosage of BTX-A used in the reported articles (range: 15 to 50 units) varied, all studies showed constant pain relief, with three studies [42, 45, 46] reporting a reduction in pain score of more than 50% from baseline. De la Torre Canales *et al.* [46] reported a notable 70% reduction in visual analog scale (VAS) score in a case involving trigeminal mandibular nerve branch (CN V3) injury where the patient did not show improvement and had poor tolerance to pharmacotherapy, including topical capsaicin, nortriptyline, pregabalin and oxcarbazepine. One of the four patients in Moreno Hay *et al.* [44] showed no improvement in postinjection pain score at 3 months.

3. Case series

A cohort of 13 patients (10 women and 3 men) were diagnosed with refractory PTNP according to ICOP criteria [1] and were seen in the Orofacial Pain Service at King's College Hospital London and St Thomas Hospital London. All patients were recruited for adjunct BTX-A injection due to their poor response or tolerance to pharmacotherapy following the NICE Guidelines for Neuropathic Pain [21] (Table 2). The mean age of the patients was 61.2 years (range 43 to 73), with the duration of PTNP prior to administering BTX-A injections ranging from 1 to 20 years. The leading cause of PTNP seen in 7 patients was post-dental extraction. Other causes of PTNP were crown restoration (2 patients), implant treatment (1 patient), endodontic treatment (1 patient), and fibroma excision (1 patient), in which all the dental procedures were performed under local anesthesia. One patient developed infraorbital PTNP after surgical implantation of sphenopalatine ganglion stimulation implantation for refractory cluster headache. Table 2 describes the patients' characteristics and their associated comorbidities. Existing orofacial pain symptoms prior to PTNP were reported by 7 of the 13 patients. Except for one case, all patients reported neuropathic pain over the region innervated by the trigeminal maxillary branch (CN V2).

Upon obtaining patients' consent, 3 to 35 units of BTX-A (Allergan Aesthetics) were injected directly subcutaneously and/or submucosally into the affected regions (Figs. 1,2, Table 3). The average BTX-A delivered across all patients was 22.2 units. The total dose of BTX-A for each patient was determined by the number of painful sites and intensity. All patients were warned of possible cosmetic facial muscle weakness after the injections. The patients were evaluated *via* phone call 2 to 6 weeks after the first BTX-A injection to ensure there were no adverse complications and to assess the efficacy of BTX-A in relieving the neuropathic pain. To evaluate the effectiveness of BTX-A in managing PTNP patients, a subjective 11-point (0–10) VAS was used to assess changes in pain scores. The BTX-A injection was repeated every 12 weeks if the pain was still present or severe.

After 3 months of review, the mean pain score of nine patients was 5.3 (standard deviation 2.4), with a significant reduction in pain intensity ($p = 0.012$) (Fig. 3). Six patients (cases 3, 4, 5, 9, 12 and 13) failed to respond to the initial BTX-A injection, and three patients (cases 3, 4 and 5) decided to discontinue the treatment. Four patients (cases 3, 4, 5 and 7) were lost to follow-up after the initial BTX-A injection due to the COVID pandemic. In the follow-ups *via* telephone, six patients (50%) (Fig. 4) reported great pain relief within 2 to 4 weeks after the initial BTX-A injection. Four patients (cases 6, 7, 10 and 11) reported a greater than 50% reduction in VAS score between 3 and 6 months of review assessment (Table 4). Six patients felt a subjective improvement in their masticatory and swallowing activities upon pain relief. In case 6, the pain intensity returned to baseline at 6 months but showed a consistent 50% reduction of VAS score in the subsequent

TABLE 1. Studies reporting the use of BTX-A in PTNP.

Study, year of publication	Study design	No. of participants	Cause of injury/duration of PTNP before BTX-A	Site/CNV branch	Sensory changes
Yoon *et al.* [43] 2010	Case report	1	Post-dental implant placement/8 mon	V3	Allodynia to light touch and hyperalgesia to cold
Cuadrado *et al.* [45] 2016	Case report	1 (3 excluded as no report of precipitating event)	Dental treatment (endodontic surgery and exodontia)/7 yr	V2	NA
Garcia-Sáez *et al.* [42] 2018	Case series	5 (4 excluded as no report of precipitating event)	Exodontia/mean: 16 yr (range: 1–37)	V2 and V3	Exacerbation of pain
Moreno-Hay *et al.* [44] 2019	Case series	4 (4 excluded, as none repor precipitating event)	Dental treatment (n = 2), exodontia (n = 1), and orthognathic surgery (n = 1)/5.8 yr	V2 and V3	Allodynia
De la Torre Canales *et al.* [46] 2020	Case report	1	Exodontia/8 yr	V3	Allodynia to light touch and hyperalgesia to pinprick

Study, year of publication (continued)	Total BTX-A dosage (units)/no. of injection cycles	Injection sites	Outcome	Adverse effects
Yoon *et al.* [43] 2010	10/1	Subcutaneously in the mid-chin area	Using Neurometer stimulation of 2000 Hz and 5 Hz; comparing the CPT between the affected (Lt) and contralateral (Rt) sides. 2 mon after BTX-A: At 2000 Hz: Lt: 33% decrease in CPT Rt: 15% increase in CPT At 5 Hz: Lt: 77% decrease in CPT Rt: 30% decrease in CPT	NA
Cuadrado *et al.* [45] 2016	25/5	Submucosa of buccal interdental gingiva papillae of painful area	Almost complete relief (mild discomfort); latency effect of 3 d Duration of analgesic effect: 4 mon Follow-up: 20 mon	No
Garcia-Sáez *et al.* [42] 2018	Mean: 18 (range: 10–25)/mean: 6 (range: 4–10)	Submucosa of buccal gingiva of painful area and dental alveoli of previous extraction site, hard palate, upper or lower lip	Baseline: Mean NRS: 8 (range: 4–10) After treatment: Mean NRS: 2.2 (range: 1–3) Mean latency effect: 7.4 d (range: 2–14) Duration of analgesic effect: 3–5 mon Follow-up: Mean: 25.4 mon (range: 12–48 mon)	No

TABLE 1. Continued.

Study, year of publication	Study design	No. of participants	Cause of injury/duration of PTNP before BTX-A	Site/CNV branch	Sensory changes
Moreno-Hay *et al.* [44] 2019	15 (range: 10–20)/1	Submucosa in the vestibular sulcus or attached gingiva of painful site	Baseline: Mean VRS: 4.8 (range: 4–6) At 3 mon: Mean VRS: 3.3 (range: 1–6) Latency effect: 7–12 d Duration of analgesic: 5–6 wk Follow-up: 3 mon		No
De la Torre Canales *et al.* [46] 2020	50/1	Intraoral submucosa of buccal gingiva	At 3 mon: VAS scores reduced from baseline, 80 to 10 Latency effect: 2 wk Duration of analgesia: 5 mon Follow-up: 6 mon		No

CPT: current perception threshold; V2: maxillary division of trigeminal nerve; V3: mandibular division of trigeminal nerve; NRS: numeric rating scale (0–10); VRS: verbal rating scale (0–10); VAS: visual analog scale (0–100); PTNP: posttraumatic trigeminal neuropathic pain; BTX-A: onabotulinum toxin A; CNV: the trigeminal cranial nerve; NA: not applicable.

TABLE 2. Clinical and demographic characteristics of patients with diagnosis of PTNP in the present study.

Patient	Age (yr)	Sex	Preceding events	Duration of pain prior to BTX-A (y)	Painful area	CNV branch involved
1	66	M	Crown restoration followed by dental extraction and implant placement	12	Maxillary right central incisor	V2
2	69	F	Crown restoration	5	Right temporal and malar region	V2
3	43	F	Dental extraction and implant placement	3	Maxillary right central incisor	V2
4	46	F	Dental extraction	2.5	Maxillary right first and second molars	V2
5	64	F	Endodontic treatment	20	Maxillary right second premolar and first molar	V2
6	62	F	Dental extraction	4	Mandibular molar extraction socket	V3
7	65	F	Dental extraction and fixed partial denture rehabilitation	1	Maxillary left premolar region	V2
8	55	F	Postsurgery of sphenopalatine ganglion stimulation implantation	1.5	Left temporal and malar region	V2
9	67	F	Dental extraction and fixed partial denture rehabilitation	8	Maxillary right gingiva	V2
10	48	F	Extraction followed by fixed partial denture	2	Maxillary left central incisor	V2
11	73	F	Crown restoration on implant	4	Maxillary left lateral incisor	V2
12	70	M	Fibroma excision under local anesthesia	2	Palate	V2
13	67	M	Implant placement	18	Maxillary left lateral incisor	V2

TABLE 2. Continued.

Patient	Age (yr)	Sex	Preceding events	Duration of pain prior to BTX-A (y)	Painful area	CNV branch involved
Patient (continued)	Medications at the time of presentation		Previous treatment(s)		Comorbidities	
1	Pregabalin, vitamin B complex		Pregabalin		Premalignant melanoma	
2	Nortriptyline, co-dydramol		Discontinued due to side effects: carbamazepine, oxycontin, fentanyl No benefit: PRF and V2 diagnostic blocks, acupuncture, lidocaine patches, lamotrigine, topiramate, gabapentin, pregabalin, morphine patches		No comorbiditiqes	
3	Pregabalin, multiple dietary supplements		For PTNP: topical anesthetic gel, naproxen		Migraine, treated breast cancer (in remission), knee pain	
4	Gabapentin, amitriptyline, vitamin B2		Carbamazepine, antibiotics, NSAIDs		Right shoulder pain	
5	Duloxetine		Discontinued due to side effects: naproxen, amitriptyline, pregabalin, gabapentin No benefit: carbamazepine, TMJ injection, cryotherapy, PRF, acupuncture		Burning mouth syndrome	
6	Pregabalin		Pregabalin		No comorbidities	
7	Dihydrocodeine Diazepam		Discontinued due to side effects: amitriptyline, nortriptyline, carbamazepine, gabapentin, pregabalin No benefit: Diclofenac, lidocaine, diagnostic nerve block: (infraorbital nerve block, anterior superior alveolar, nasopalatine nerve block)		Fibromyalgia, episodic migraine, hypercholesterolemia, menopause	
8	Amitriptyline		Levetiracetam, indomethacin, pregabalin		Left-side chronic cluster headache, Sjogren syndrome, sphenopalatine ganglion stimulation *in situ*	
9	Lamotrigine Ibuprofen Vitamin B & D		Pregabalin, co-codamol, Paracetamol, mouth lotion, acupuncture		No comorbidities	
10	Pregabalin		Not reported		Gastric reflux	
11	Propranolol		Not reported		Migraine	
12			No benefit: pregabalin		Glossopharyngeal neuralgia	
13			No benefit: gabapentin, pregabalin		Diabetes mellitus type 2, hypertension, bruxism	

V2: maxillary division of trigeminal nerve; V3: mandibular division of trigeminal nerve; PRF: pulsed radiofrequency; NSAIDs: nonsteroidal anti-inflammatory drugs; M: Male; F: Female; BTX-A: onabotulinum toxin A; CNV: the trigeminal nerve; TMJ: temporomandibular joint.

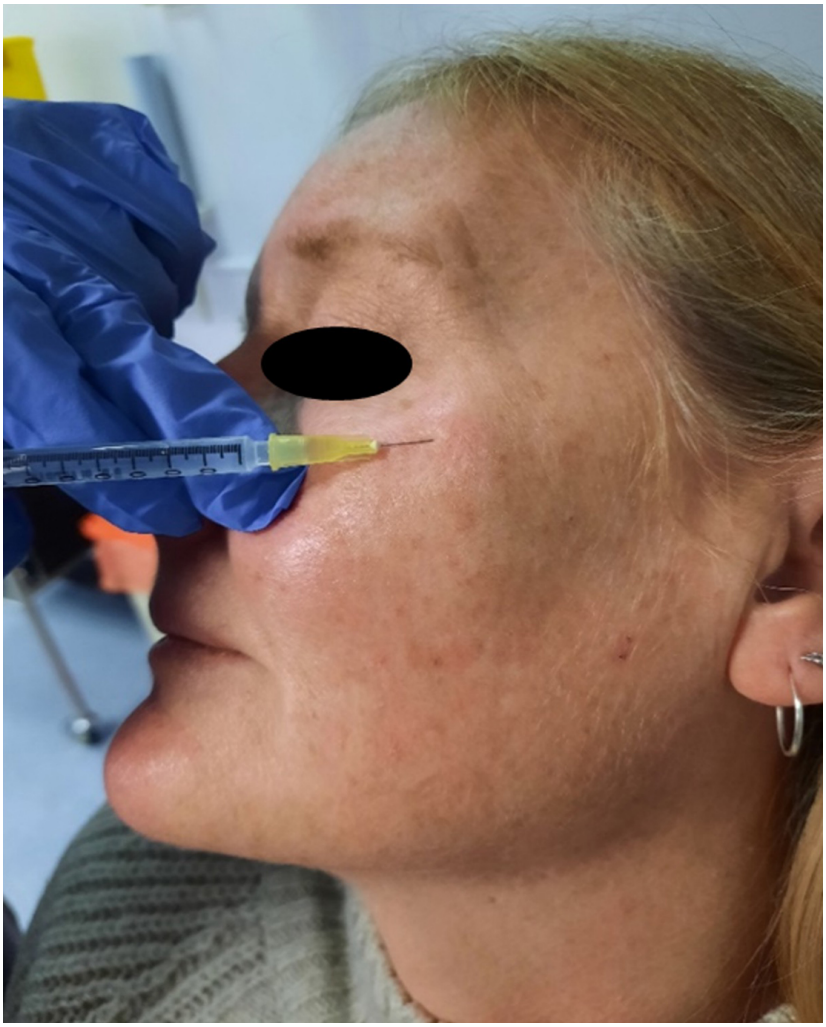

FIGURE 1. Subcutaneous injection of BTX-A in the left zygomatic-buccal region.

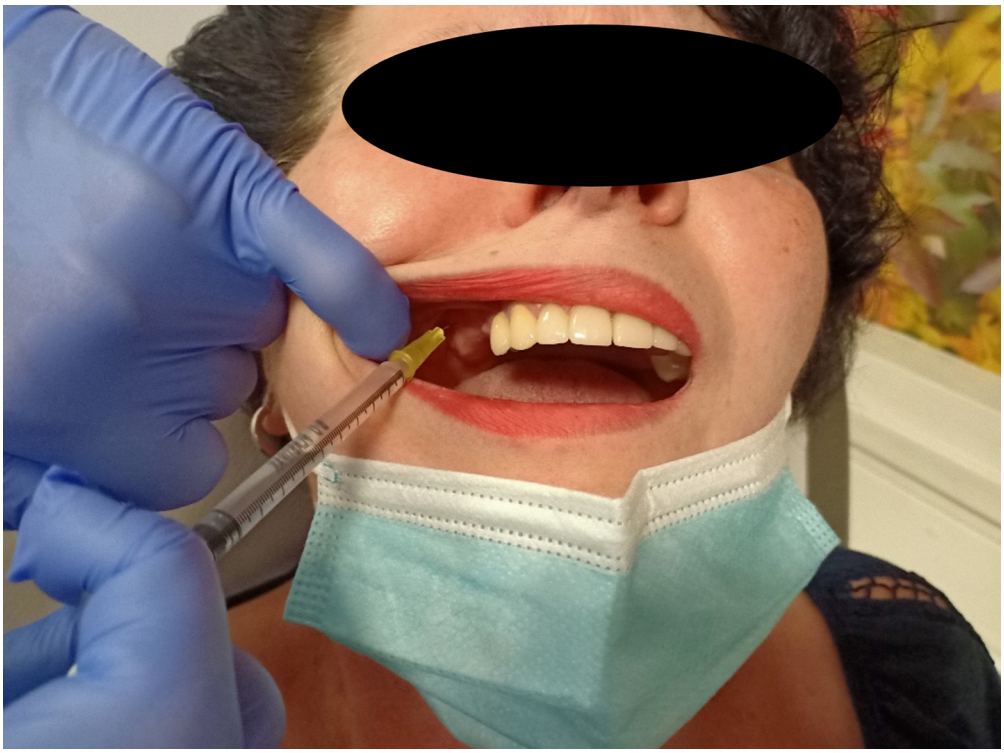

FIGURE 2. Intraoral submucosal injection of BTX-A in the maxillary right molar region.

TABLE 3. BTX-A Administration.

Patient	Site of injection	Mean BTX-A dose (units)	No. of injections	Patient-reported benefit(s)/outcome(s)	Adverse effect(s)
1	Right anterior hard palate	25	2	Reduction in the intensity of pain after the first injection.	Uncomfortable feeling and no improvement after the second treatment.
2	Maxillary right gingiva	25	3	Reduction in the intensity of pain after two injections. No significant improvement after the third injection.	No complications reported.
3	Anterior maxillary region	50	1	No improvement after the first treatment.	No complications reported.
4	Maxillary right first molar	30	1	No improvement after the first treatment.	An increasing intensity of the burning sensation.
5	Maxillary right second premolar and first molar region	30	1	No improvement after the first treatment.	No complications reported.
6	Mandibular right second molar (mesiobuccal) and second premolar (distobuccal)	17.9	7	Reduction in pregabalin dosage. Improved symptoms significantly.	One episode of transient facial weakness with drooping of the right angle of the mouth during the first BTX-A injection with no functional disturbance. No complications with subsequent injections.
7	Left anterior superior alveolar nerve	25.2	12	Reduction in the intensity of pain.	One episode of transient facial weakness with drooping of the left angle of the mouth and cheek during the first BTX-A injection with no function disturbance. No complications with subsequent BTX-A injection.
8	Left zygomatico-buccal, zygomatico-temporal, and auriculotemporal nerves	25	2	Reduction in the frequency of pain attacks.	No complications reported.
9	Right anterior and middle superior alveolar nerve regions	25	1	No improvement.	Right facial drooping. No improvement post BTX-A injection.
10	Maxillary left central incisor and balancing injection on the right side	7	1	Significant improvement after 2 wk. Reduction in pain intensity. Patient is still on pregabalin.	No complications reported.
11	Palatal side between maxillary left central and lateral incisors	3	1	Remarkable improvement after 1 wk. Reduction in pain intensity.	Pins-and-needles sensation on upper lip radiating to left eye for 2 d after injection.
12	Former excisional site at palate	5	1	No benefit.	No complications reported.
13	Maxillary left lateral incisor and balancing injection on the right side.	20	1	No benefit.	No complications reported.

BTX-A: onabotulinum toxin A.

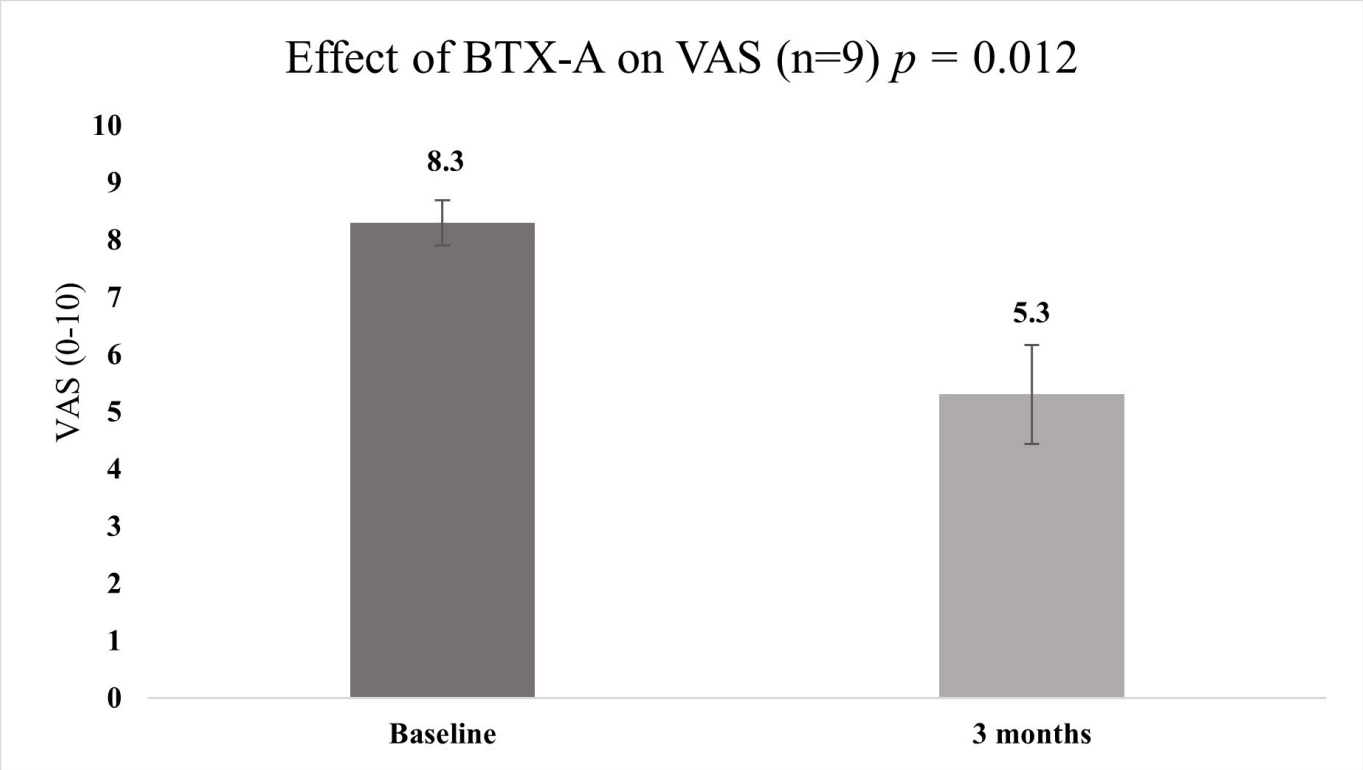

FIGURE 3. Effect of BTX-A on pain scores at 3-month follow-up.

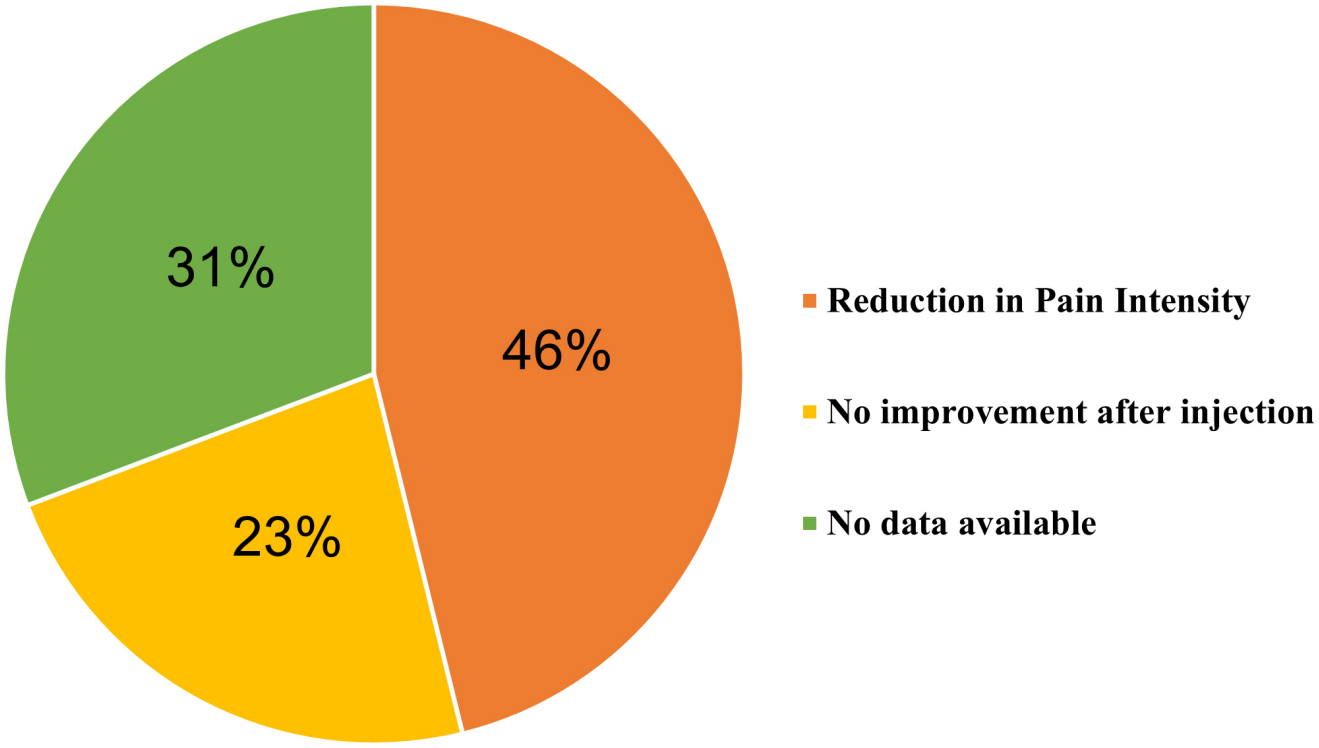

FIGURE 4. Outcomes of BTX-A administration after 3 months.

TABLE 4. Patient VAS scores and pain characteristics.

Patient	Pain symptoms	Mean VAS score (0–10)							
		Baseline	3 mon	6 mon	9 mon	1 yr	2 yr	3 yr	5 yr
1	Burning feeling	7	5	–	–	–	–	–	–
2	Numbness, tingling, and nagging pain	9	6	8	–	–	–	–	–
3	Throbbing or pulsating pain, occasionally with an electric shock	8	–	–	–	–	–	–	–
4	Very severe and continuous throbbing, burning, and stabbing	7	NA	–	–	–	–	–	–
5	Cold hitting the tooth	10	NA	–	–	–	–	–	–
6	Burning sensation	9	4	10	4	5	4	1–2	–
7	Toothache pain, occasional stabbing pain	9	NA	4	–	2	2	2	2
8	Cold allodynia	9	5	5	–	–	–	–	–
9	Dull ache, shooting and throbbing when severe	9	9	–	–	–	–	–	–
10	Acute shooting pain, mechanical allodynia	10	2	–	–	–	–	–	
11	Spontaneous shooting pain, mechanical allodynia and hyperalgesia	7	2	–	–	–	–	–	–
12	Elicited mechanical allodynia and hyperalgesia	8	8	–	–	–	–	–	–
13	Tingling sensation and stinging feeling	7	7	–	–	–	–	–	–

VAS: visual analog scale; NA: not applicable; yr: year.

visits. Cases 6 and 7 received regular BTX-A therapy for 3 years at 3-month intervals, reporting an overall 80% pain score reduction. There was no statistically significant correlation between changes in VAS score after BTX-A administration and the pain duration and baseline pain scores.

Three patients reported transient partial hemifacial paralysis after BTX-A injections; 5 to 10 units of BTX-A were injected at the contralateral site to address the undesired cosmetic adverse effect and to prevent facial asymmetry. Two patients developed somatosensory changes after BTX-A treatment. One patient reported sharp shooting ipsilateral pain around the nostril and eye after 3 months, and another patient experienced a pins-and-needles sensation radiating to the ipsilateral nostril and eyes for 2 days after injection. None of the patients reported experiencing any serious adverse effects from long-term BTX-A therapy.

4. Discussion

The IASP defines neuropathic pain as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [47]. Persistent dentoalveolar pain (PDAP), which was previously thought to be PTNP, was excluded from the present case series and literature review based on the ICOP definition of PTNP [1]. PDAP is an idiopathic neuropathic pain and is not secondary to trauma, while PTNP is an orofacial pain that occurs due to mechanical, thermal, radiation or chemical trauma of the trigeminal cranial nerve (CN V) and its branches. The severity of the nerve injuries may range from negative signs, such as anesthesia, to mild or severe dysesthesia over the injured dermatome distribution [2]. The burdens in managing chronic PTNP patients include their inconsistent pharmacotherapy response, poor drug tolerance, and high gabapentanoid drug number-to-treat (pregabalin: 7.7; gabapentin 6.3) [17].

The mechanism of neuropathic pain in peripheral and central nervous systems is complex, and key interactions within sensory pathways have been discovered, but no common molecular mechanism leading to neuropathic pain has been identified [48, 49]. An overview of the pathophysiology of trigeminal PTNP has recently been published [50].

The suppressive action of BTX-A on the trigeminal nociceptive system was demonstrated in a study in which BTX-A inhibited pain conduction after intradermal injection of capsaicin in the forehead [51]. In addition, an *in vivo* study on the trigeminal ganglion in rats showed the antinociceptive role of BTX-A [52]. It was thought that BTX-A suppressed the release of peripheral and central allogenic neurotransmitters, thus promoting analgesia [53]. Upon injury to the nerve, neurotransmitters involved in pain modulation were released. The antinociceptive effect of BTX-A is hypothesized to be related to its ability to inhibit the release of noncholinergic neurotrans-

mitters and nociceptive mediators, such as substance P and calcitonin gene-related peptide (CGRP), and the expression of transient receptor potential vanilloid-1 (TRPV1), which are associated with neurogenic inflammation and peripheral sensitization [54–56] at the injured site. This inhibits the transmission of nociceptive impulses from the primary peripheral injured site to the central nervous system [57]. Upon injections of BTX-A at the painful neuropathic site, the toxin will be taken up by the peripheral terminals of nociceptive afferent nerve fibers [58]. This suggests a local peripheral effect of BTX-A on the cutaneous nociceptors [51] and the possibility of BTX-A as an adjunct therapeutic peripheral nerve block against chronic intractable neuropathic pain [59]. For immediate relief of pain arising during injection and better pain reduction efficacy, a mixture of BTX-A and local anesthetic was administered without a vasoconstrictor, such as adrenaline, to allow a wider toxin diffusion and uptake area.

Poor patient drug compliance was reported in a previous study, with less than 45% of patients continuing their treatment [60]. Inadequate therapeutic response to medication may be due to a lack of motivation, the preference for a quick fix for the problem [61, 62], medication intolerance, which is likely psychosomatic [63], and medication sensitivity, which prevents the patient from achieving an optimal therapeutic dosage to manage their pain without side effects [64–66]. Thus, psychologic behavior assessment prior to treatment could assist in identifying candidates with poor oral drug compliance who may benefit from BTX-A therapy. There is recognition that patient vulnerability is a crucial issue, reinforcing the need for holistic assessment and management of pain [67]. As PTNP is a debilitating disorder, it could greatly affect patients' psychosocial function and oral health.

Phenotyping the patient's pain [2, 3] diagnosis as PTNP is important for further stratifying (endotyping) PTNP patients based on their pain characteristics [68, 69] as a responder or a nonresponder to BTX-A therapy. Attal *et al.* [70] reported that patients with mechanical allodynia and thermal deficit ($p < 0.05$) symptoms were valuable predictors in profiling patients as responders to BTX-A. A study in patients with neuropathic pain arising from different causalities has classified patients into three groups: pinprick pain (paresthesia); deep pain; and elicited mechanical allodynia. Patients in the deep pain or allodynia groups responded better to BTX-A therapy than the paresthesia group [71], and this benefits PTNP patients, as they often present with mechanical and thermal hypersensitivity [70, 71]. This was reflected in the present case series, where six of nine patients with a history of continuous pain or allodynia reported improvement in their pain at 3 months. Hence, the importance of somatosensory assessment before a clinical decision on BTX-A administration must be stressed.

A diagnostic peripheral nerve block (PNB) may be helpful for ascertaining a favorable patient response to BTX-A therapy, but limited evidence is available to support the screening of patients using local anesthetic nerve blocks [72]. It is believed that delivery of PNB at the specific peripheral sensory nerve distribution of the pain site interrupts the transduction or transmission of nociceptive action potential from the peripheral nerve branches to the central nervous system. Due to the lack of evidence on using PNB in determining BTX-A prognosis responses and the additional injection discomfort to the patient, this was not performed in the present authors' center.

A consensus on the therapeutic dosing range of BTX-A for achieving an ideal therapeutic result while reducing the adverse effects could not be found. The dosage varies and is dependent on the clinician's choice and the patient's subjective pain intensity during the review visits. The total dosage of BTX-A used in the authors' clinical practice was comparable to the five case reports in the literature review.

The effectiveness and safety of repeated BTX-A injections have been reported in other peripheral neuropathic pain [70] studies. A placebo-controlled randomized trial of 68 patients with peripheral neuropathic pain (the patient population was not restricted to this condition, but two-thirds of the patients did have PTNP) published promising results on the efficacy and safety of repeated BTX-A injections [70]. The improvement was insignificant after the first BTX-A injection compared to the placebo group, but the pain intensity significantly improved 6 months after the second injection compared to the placebo group ($p < 0.0001$). Repeated regular BTX-A injections for neuropathic pain have been shown to be safe while increasing the therapeutic benefits of BTX-A [42, 45]. The sustained pain relief derived from repetitive BTX-A injection was reflected in two case series patients with follow-ups of 3 and 5 years, respectively. Prolonged BTX-A therapy may increase the duration of analgesia response, and patients may need less frequent BTX-A administration and a lower BTX-A concentration [73]. The accumulative chemo-denervation effect of BTX-A injections has been shown to be superior to single use against peripheral neuropathic pain [42, 70]. The only unpleasant event noted in the present case series was pain during BTX-A injection, but studies have shown no significant difference in pain during injection between placebo and treatment groups ($p = 1.0$) [70]. However, long-term use of BTX-A may result in the development of a tolerance to BTX-A, resulting in a loss of its antinociceptive sensory effect [74]. To avoid the possibility of untoward long-term BTX-A adverse events and the development of sensitization to BTX-A in its treatment for headache and migraine, administration of the minimum effective antinociceptive BTX-A dosage and minimizing the frequency of booster injections, with an interval of at least 3 months once achieving constant pain relief, were practiced [38].

The use of BTX-A has been viewed as safe, with a low risk of severe adverse events if a thorough medical history is obtained and with the practice of an appropriate dosage and injection technique. The side effects of BTX-A could be classified as transient, well localized, reversible complications or as potentially serious systemic botulism events [75]. Common transient BTX-A side effects, including pain, edema, erythema, ecchymosis and hypoesthesia, could occur immediately or not until days after treatment [75]. Concerns of botulism in the orofacial region include the risk of dysphagia, dysphonia, diplopia, breathing difficulties, and anaphylactic allergic reaction to BTX-A. This is reflected in the present case series, where no patients experienced any permanent loss of orofacial muscle function or systemic toxicity with repeated use of BTX-A. It is advised to caution patients regarding

the possible migration of the toxin from the injection site to a broader area, which may cause localized transient facial muscle paralysis. There is insufficient documentation on the adverse effect of BTX-A—induced muscle atrophy in prolonged repetitive administration of botulinum toxin injection [76] in chronic neuropathic pain. Factors contributing to BTX-A—induced muscle atrophy were types of botulinum toxin, advanced age, gender, muscle reinnervation and characteristics, underlying comorbidities, muscle spindles, blood perfusion, and fat volumes [76]. It has been hypothesized that systemic adverse effects could occur due to accidental intravenous injection of BTX-A [77] or retrograde transport of the toxin to the nerve cell bodies [78].

The submucosal intraoral injection is safe and easily delivered in the buccal vestibule, gingiva and hard palate, as practiced in the present authors' center. The side effects were minimal, with the most commonly reported being transient cosmetic facial asymmetry mainly due to unilateral application of the drug. A contralateral BTX-A injection [79] or injection of BTX-A into facial muscles that antagonize the affected muscles [75] could address this issue. An improper intraoral injection technique may lead to diffusion of BTX-A to adjacent salivary glands, causing xerostomia, which has been reported in a persistent dentoalveolar pain study [41]. Clinicians should be cautious about the adjacent vital structures that are highly perfused and have motor nerve innervation, such as the tongue, floor of the mouth, and soft palate. This may lead to grave systemic toxicity events. The use of a vasoconstrictor could help localize the effect of BTX-A by limiting the diffusion of BTX-A to adjacent vital structures. However, this may also reduce the analgesic efficacy and distribution of BTX-A, and multiple injection sites may be needed, as the pain or trigger zones are often not localized to a single point of the traumatic nerve dermatome innervation.

As reported in the present case series and in the literature, combined submucosal and subcutaneous BTX-A injections have effectively treated intraoral PTNP [42, 44–46]. Submucosal BTX-A injection over the pain or trigger zones concerning the distribution and innervation of the injured maxillary or mandibular branches of the trigeminal nerve has displayed a similar analgesic latency period compared to subcutaneous administration, at between 1 and 2 weeks post-BTX-A injection [41–43, 46], except for one study reporting a 3-day latency period [45]. The analgesic effects of BTX-A were reported to continue for 2 to 5 months [41, 42, 44–46]. Studies have reported that three monthly intraoral BTX-A injection cycles (*i.e.*, one injection a month) have a higher percentage of pain relief (70%) [41, 42, 45], as seen in cases 6 and 7. The therapeutic BTX-A range in the present case series falls within the literature's reported submucosal BTX-A injection dosage, between 10 and 50 units [41, 42, 44–46].

Based on this retrospective case series and literature review, the use of BTX-A in refractory PTNP patients has greatly improved pain control and enhanced mental and physical health. This would reduce the need for polypharmacy treatment and the risk of adverse drug reactions, including cognitive and motor impairment and drug-to-disease interactions. The major caveat is that the use of BTX-A in chronic neuropathic orofacial pain is "off label". Reports on BTX-A as a potential PNB for treating PTNP are encouraging, but there is no high-quality evidence to conclude that BTX-A injections can become a standardized treatment for refractory PTNP. The literature supporting its efficacy in many of these conditions is weak, consisting mainly of a case report or uncontrolled, open-label studies rather than double-blinded randomized clinical trials. In addition, patient profiling and selection before BTX-A treatment are crucial.

5. Conclusions

Although the quality and evidence level of the published literature were low, the benefits of BTX-A for treating refractory PTNP are compelling. BTX-A may be beneficial as an adjuvant treatment option for patients suffering from neuropathic pain with a peripheral component presenting intraorally and involving the dentoalveolar areas. The relative safety profile of BTX-A allows for repetitive BTX-A injections to achieve continuous pain relief, which will improve patients' psychosocial function. However, these findings should be interpreted cautiously due to the poor evidence quality. A large-scale randomized controlled trial is suggested to assess the safety and effectiveness of BTX-A as an antinociceptive agent in treating painful refractory PTNP. A regulated guideline on using BTX-A in managing PTNP is essential to achieve the best effect while minimizing any unknown long-term adverse effects.

6. Highlights

Botulinum toxin may be a novel intervention for refractory PTNP.

The potential use of BTX-A as an adjunct therapy may reduce the need for polypharmacy in managing neuropathic pain symptoms.

Large and well-designed randomized controlled clinical trials are needed to support BTX-A injection as a relatively safe repetitive therapy for the long-term management of patients with chronic PTNP.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

TR—designed the research study. TR, HLT and PY—performed the research. HLT and PY—analyzed the data and drafted the manuscript. TR and AB—provided critical revisions to the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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