Onabotulinum Toxin A Treatment for Post-Traumatic Trigeminal Neuropathic Pain: Case Series and Literature Review.

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Abstract

Introduction: ~~Post-traumatic trigeminal neuropathic pain (PTNP) is a common injury of the trigeminal nerve caused by dental procedures. (Please reword this sentence; there is erroneous connotation of pain being the same as injury. PTNP: what classification are the authors following? ; please review the statement that "it is common"; also are dental procedures the only etiological factor? Can trauma cause it?) The unmanageable pain, traumatic experience, imprecise diagnosis, and multiple drug prescriptions significantly impact the patient's quality of life. (Consider changing "significantly", since this word may denote statistical significance) Onabotulinum Toxin A (BTX-A) has demonstrated therapeutic benefit in managing other trigeminal neuropathic pain but is not established in PTNP.~~

Up to 70% of patients with trigeminal nerve injuries sequentially to traumatic dental procedures will develop chronic post-traumatic trigeminal neuropathic pain (PTNP). The refractory pain, traumatic experience, imprecise diagnosis, and polypharmacy greatly impact the patient's quality of life. Onabotulinum Toxin A (BTX-A) has demonstrated therapeutic benefit as an adjunctive treatment in managing neuropathic pain but is not established in PTNP.

Aim: The study aims to assess the treatment outcomes of BTX-A on a series of refractory ~~13 patients with~~ PTNP patients in our centre. ~~that previously not responding to medication.~~ A narrative review of the evidence for BTX-A in PTNP is provided.

Methods: Thirteen patients were treated with BTX-A infiltrations. ~~Patients' demographics (please reword grammar into "demographics of the patients"),~~Patients' demographic and pain characteristics, BTX-A administration, and treatment outcomes were retrospectively analysed ~~reviewed~~. Resultant papers retrieved after a literature search of articles citing ~~treatment of~~ PTNP treatment using BTX-A were reviewed. ~~and analysed.~~

Results: ~~One patient reported 50% and two patients with 80% pain reduction after single or repeated BTX-A injections and improved daily activities. Three patients reported facial asymmetry, and all except one proceeded with repeat injections with balancing injections, where required.~~ Six patients reported improvement in pain three months after the initial BTX-A injection, with four patients reporting a 50% reduction. Two patients achieved an 80% reduction in pain score over three 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, which reported similar effectiveness to our cohort study.

Conclusion: BTX-A may ~~have be~~ be a potential treatment modality for refractory PTNP, thus reducing ~~and reduce~~ the need for polypharmacy. ~~(please reword the sentence to correct grammar).~~ Multiple ~~sites~~ intraoral BTX-A injections administered over the pain sites are well tolerated, ~~easy and~~ safe, and easily ~~to be~~ practised~~ce~~. ~~(please reword the sentence to correct grammar)~~ ~~However, h~~High-quality studies are required to evaluate the long-term therapeutic efficacy and side effects of BTX-A therapy.

Keywords: traumatic trigeminal neuropathy, trigeminal neuropathy, neuropathic pain, submucosal, botulinum toxin

Introduction

~~Multiple factors that could contribute to the development of peripheral neuropathy include trauma, viral or bacterial infection (e.g., Herpes Zoster, Herpes Simplex, Epstein Barr virus, HIV and Lyme disease), metabolic diseases (e.g., diabetes mellitus, hypothyroidism, nutritional deficiencies), autoimmune disorders (e.g., rheumatoid arthritis, Lupus, polyneuropathy), genetic disorders (e.g., Charcot Marie Tooth disease) and tumours invasion (correct grammar). During surgery (in the abstract, the authors state the cause is "dental procedures". Please specify, supported by appropriate citations, if it is during surgery, other dental procedures, or can it be also due to accidental and incidental trauma?) , damage to the peripheral nervous system may lead to painful sensory neuropathy, and is commonly reported within, [1,2] and outside the trigeminal system [3,4]. Post-traumatic neuropathy is limited to patients whose sensory neuropathy has been caused by trauma (mechanical, chemical, or thermal). The International Classification of Orofacial Pain (ICOP) [5] has set out diagnostic criteria, which includes demonstrating a neuropathic area that coincides with the anatomical area where the trauma occurred and development of neuropathy within six months (radiation and chemotherapy causation), with associated positive or negative signs. Positive signs include burning, sharp or shooting pain, often with allodynia (mechanical~~

or thermal), hyperalgesia and hyperpathia [5]; this concords with the International Classification of Headache Disorders (ICHD-3) [6]. Finnerup NB et al. has summarised and revised the grading system by the International Association for the Study of Pain (IASP) Special Interest Group on Neuropathic Pain (NeuPSIG) on the level of certainty in diagnosing possible, probable, and definite neuropathic pain [7]. These are applied to the trigeminal system injury, in which clinical neurosensory examination is vital in determining a diagnosis of probable neuropathic pain? [8].

Dental procedures are high volume (what does high volume mean?), with an estimated two million mandibular third molar extractions undertaken in the UK alone per year [9]. All surgical procedures carry a risk of sensory nerve injury [10], and several reviews have highlighted the possible prevention and management of PTNP concerning dental surgery [11,12]. Post-traumatic peripheral neuropathic pain may not be life-threatening but could cause a remarkable impact on a patient's quality of life [13,14]. It is also suggested that trigeminal pain presents a significantly higher effective component (please explain the term "effective component") than other regional pain [15]. The iatrogenic nature of pain caused by surgery also adds to the affective burden [14,15]. Chronic PTNP in the orofacial region impeded essential daily functions, including the patient's speech, mastication, and swallowing function, with a reported significant psychosocial burden in these patients [2].

There are many published international guidelines on managing patients with neuropathic pain by various task forces such as the National Institute for Health and Care Excellence, UK (NICE), European Federation of Neurological Societies, German Society of Neurology and American Academy of Pain Medicine. These task forces suggest multidisciplinary treatment using psychological, medical pharmacological?, and rarely surgical management [16-20].How about adjunctive therapy? The NICE guidelines recommends the non-specialist's role in managing neuropathic pain in adults with pharmacological treatments [20]. The mainstay of treating patients with affected by neuropathic pain is systemic and topical medications using tricyclic antidepressants and gabapentinoids, with their attendant side effects resulting in poor patient compliance [21-23]. Thus, medication is often ineffective in managing patients with PTNP, and other strategies are needed [1]. There is high-level evidence for the

~~therapeutic value of OnabotulinumtoxinA (BTX-A) as a peripheral prophylactic or symptomatic therapeutic nerve block for neuropathic pain [24] (this statement seems to be totally erroneous based on the citation 24. The evidence in this referenced manuscript is "low" or "N/A". Also, please explain what the authors meant by "prophylactic"? Is BTX-A used as a prophylactic treatment for neuropathic pain?) with a level A evidence on the use of BTX-A in treating trigeminal neuralgia [25-27] (Cited references 26 and 27 do not seem to mention the "level of evidence". Please cross check) and post-herpetic neuralgia [28,29] (Cited references 28 and 29 do not seem to mention the "level of evidence". Please cross check), level B evidence in treating post-traumatic and painful diabetic neuropathic pain [25], and with lower-level evidence supports the use of BTX-A for orofacial musculoskeletal disorders such as myofascial pain or hyperactivity [30-32], cervical dystonia [33,34]. In addition, BTX-A is relatively safe with reversible effects and is a one of the recommended therapies for headache [35] and migraines [36-39]. BTX-A is injected into the painful neuropathic location, and the toxin is taken up by the peripheral terminals of nociceptive afferent nerve fibres. (citation?) This action suppresses the peripheral and central release of allogenic neurotransmitters, thus promoting analgesia [40]. However, there is limited evidence available with regards to treating trigeminal PTNP with BTX-A. Two case reports were using BTX-A for peripheral PTNP [41,42]. (please correct grammar) Both Herrero BA et al. and García-Sáez R et al. treated their patient with intraoral botulinum toxin injections [41,42]. (rephrase the sentence so as to avoid doubling citations inside the sentence and at the end) The patients in these articles studies were diagnosed with orofacial neuropathic pain that was non-responsive to previous, commonly prescribed treatments. (What treatments were unsuccessful?) The BTX-A is introduced as an addition to their therapy. (Correct grammar. Be consistent with the tense) The results of these case reports are promising, as the patients lost a considerable amount of pain. (Please rephrase the sentence to proper English) In other words, the intensity and frequency of the pain lowered considerably, which made the patients feel more comfortable than before. (Please delete layman versions of language) As a result, (Suggest restarting the sentence: "Here we attempt…") we embark on a retrospective analysis of 13 patients that we have treated and a review of the current literature on the use of botulinum toxin in PTNP.~~

Post-traumatic 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 post-traumatic neuropathy as a neuropathic site that coincides with the anatomical area where the trauma occurred and is followed by neuropathy development within six months and has associated somatosensory changes. Positive neuropathic signs include burning, sharp or shooting pain, allodynia (mechanical or thermal), hyperalgesia and hyperpathia[1] and this concords with the International Classification of Headache Disorders (ICHD-3)[2]. Finnerup NB et al.[3] have further summarised 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, emphasising 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 anaesthesia (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 two million mandibular third molar extractions undertaken in the UK per year[6], several reviews have highlighted the prevention and management of post-traumatic peripheral trigeminal neuropathic pain (PTNP) concerning dental surgery[7,8]. 70% of the nerve injuries 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[14,15,16]. It is suggested that orofacial trigeminal pain has a higher affective component impact on patient psychosocial function than other regional pain[15]. Chronic PTNP in the orofacial region also impeded essential daily functions, including the patient's speech, mastication, and swallowing[11].

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

These task forces suggested the importance of multidisciplinary treatment, including psychological, pharmacological, adjunct therapy such as neurostimulation and rarely surgical intervention[17-21]. The NICE guideline also detailed the importance of non-specialists' role in pharmacological managing adults' neuropathic pain [21]. The primary recommendations for treating patients with neuropathic pain are systemic and topical drugs using mainly tricyclic antidepressants and gabapentinoids, with their attendant side effects resulting in poor patient compliance[22-24]. Thus, pharmacotherapy is often ineffective in 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 Onabotulinumtoxin A (BTX-A) was demonstrated in trigeminal neuralgia[27-29], post-herpetic neuralgia[30,31], post-traumatic neuralgia[27,32], post-surgical 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 in treating intraoral neuropathic pain were 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. Here we attempt to retrospectively analyse 13 PTNP patients that we have treated with BTX-A and review the literature on the use of BTX-A in PTNP.

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'. ~~The literature search was limited to English text (Articles in English?), and patients must have a description of precipitating events before and related to the diagnosis of PTNP to be included in this review. (Rephrase the sentences; what the author means is not clear at all) Persistent dentoalveolar pain was excluded.~~ Articles in the English language that described the causation events of 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] ~~on BTX-A in PTNP~~. The ~~patients'~~ clinical characteristics of patients ~~(Suggested: The clinical characteristics of the patients)~~ and the treatment modalities ~~were ("are")~~ are summarised in Table 1. All included patients received first-line pharmacology treatment but responded poorly to it, except for Yoon et al.[43] who,~~., who~~ reported a 60% decrease in dysesthesia ~~in the patient~~ but failed to achieve ~~significant~~ continuous pain-free episodes following six months of pharmacotherapy.[43]~~.~~ The primary cause of trigeminal maxillary or mandibular nerve branch injuries wasere dental treatments or surgeries such as dental exodontia, implant, endodontic, and orthognathic surgery. ~~followed by orofacial surgical procedures. (Please specify the dental treatments and the surgical procedures) Four studies reported no adverse effect associated with post-BTX-A injection [42,44-46], and four studies [42-44,46] reported the presence of sensory changes in patients such as allodynia and hyperalgesia. (Please correct grammar) Despite (Please avoid layman language) the various dosage of BTX-A used in the reported cases (range: 15 to 50 units), all cases showed consistent significant pain relief, with three studies [42,45,46] reported more than 50% pain score reduction from baseline.~~ No serious adverse effect was reported in four studies after BTX-A injection [42,44-46], but patients experienced sensory changes such as allodynia and hyperalgesia. Although the dosage of BTX-A used in the reported articles (range: 15 to 50 units) varies, all studies showed constant pain relief, with three studies[42,45,46] reported more than 50% pain score reduction from baseline. De la Torre Canales G et al.[46] reported a notable 70% reduction of VAS score in a case ~~of PTNP~~ involving trigeminal mandibular nerve ~~mandibular~~ branch (CN V3) injury, which did not show ~~any~~ improvement and had poor tolerance to pharmacotherapy, including topical capsaicin, nortriptyline, pregabalin and oxcarbazepine. One of the four patients in Moreno Hay I et al.[44] showed no improvement in its post-injection pain score at three months. ~~with pharmacotherapy [46]. (Type of pharmacotherapy? Please avoid doubling the citations) One of the four patients in Moreno Hay I et al. showed no improvement in its post-injection pain score at three months [44], (Please avoid doubling the citations) and this similarity is observed in our case study 4.~~

Case Series

~~A prospective cohort of patients seen in the Orofacial Pain Service at Kings College Hospital London and St. Thomas Hospital London was diagnosed with neuropathic pain in accordance with ICOP diagnostic criteria[5] and had responded poorly to first-line medical management for their pain following NICE Guidelines for Neuropathic Pain UK [20]. (Please correct grammar and punctuations) Ten female and three male patients with a mean age of 61.2 years (range 43 to 73) were diagnosed with refractory PTNP under ICOP criteria [5]; all had limited pain relief or could not tolerate the anti-neuropathic medication. (What was the drug?) The duration of PTNP ranged widely from one to twenty years before the (Suggested: prior to the utilization of) BTX-A injections. The leading cause for PTNP in seven patients was post-dental extractions. (Please correct grammar)~~ A cohort of 13 patients (ten females and three males) 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 the patients were recruited for adjunct BTX-A injection due to their poor response or tolerance to pharmacotherapy following the UK 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 ranging from one to twenty years prior to administering BTX-A injections. The leading cause of PTNP seen in seven patients was post-dental extractions. Other causes of PTNP ~~causes~~ 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 anaesthesia. One patient developed infraorbital PTNP after surgical implantation of sphenopalatine ganglion stimulation implantation for refractory cluster headache. Table 2 describes the patients' characteristics ~~patients' characteristics~~ and their associated comorbidities. ~~(Please correct grammar)~~ Existing orofacial pain symptoms prior to PTNP were reported by seven of the 13 patients. Except for case 6, all patients reported neuropathic pain over the region innervated by the trigeminal maxillary branch (CN V2).

~~After obtaining the patients' consent, (Please correct grammar) between 3 and 35 units (What was the basis of selecting from this wide range of dosage units? Rationale for the variation in the units)~~ Upon obtaining patients' consent, 3 to 35 units of BTX-A (Onabotulinum Toxin A®, Allergan, Irvine, CA, USA) were injected directly subcutaneously or/and submucosally into the affected regions (Figure 1,

Figure 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 ~~asymmetry~~ after the ~~initial~~ injections. The patients were evaluated via phone call two to six weeks after the first BTX-A injection to ensure no adverse complications and assess the efficacy of BTX-A in relieving the neuropathic pain. ~~The patients' pain reduction was assessed with an 11-points visual analogue scale (VAS). (Please correct grammar) The BTX-A injection was repeated every 12 weeks depending on the severity of their pain when the BTX-A analgesic effect had worn off. (Does BTX-A has analgesic effect? Citations? And, do the authors mean local anesthetic?)~~ To evaluate the effectiveness of BTX-A in managing PTNP patients, a subjective 11-points (0-10) visual analogue scale (VAS) was used to assess changes in pain scores. The BTX-A injection was repeated every 12 weeks, depending on the pain severity.

After three months of review, the mean pain scores of nine patients were 5.3 (SD ± 2.4), with a significant reduction in pain intensity (p= 0.012) (Figure 3). Six patients (cases 3,4,5,9,12,13) failed to respond to the initial BTX-A injection, and three patients (cases 3,4,5) decided to discontinue the treatment. Four patients (cases 3,4,5,7) lost follow-up after the initial BTX-A due to the COVID pandemic. In the telephone reviews, six patients (50%) (Figure 4) reported great pain relief within two to four weeks after the initial BTX-A injection. Four patients (cases 6,7,10,11) reported a greater than 50% reduction in VAS scores between three to six 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 six months but showed a consistent 50% reduction of VAS scores in the subsequent visits. Cases 6 and 7 received regular BTX-A therapy for three years at three-month intervals, reporting an overall 80% pain score reduction. There was no statistically significant correlation between changes in VAS scores after BTX-A administration and the pain duration and baseline pain scores.

~~Three patients (cases 3,4,5) failed to respond to the first BTX-A injection and discontinued the treatment. However, the other three patients (cases 9,12,13), who did not respond to the first injection,~~

~~aimed to continue with the subsequent BTX-A treatment. At telephone review, six patients (50%) (Figure 3) reported subjective significant pain relief within two to four weeks following the first BTX-A injection. Four of them (cases 6,7,10,11) reported a more than 50% reduction of VAS scores (Expand VAS: first time being used) from the baseline between three to six months of assessment (Table 4). However, in case 6, the pain intensity increased to baseline at six months but showed a subsequent consistent 50% reduction of VAS score in following visits. Case 6 and 7 received constant BTX-A therapy for three years at three-month intervals, reporting an 80% baseline pain score reduction. The initial analgesic effect (latency period) (This statement is ambiguous; please explain what the authors mean by "analgesic effect" and "latency period") was felt between one to two weeks post-injection, and the analgesic effect lasted between one to (Please correct grammar) three months before returning to pre-BTX-A levels or raise of higher pain score. After three months of review, all six patients with pain reduction reported improved ability to perform daily functional activities, especially mastication, drinking, and swallowing. (Please compare with the pre-injection functional levels of all these actions; are the authors differentiating between drinking and swallowing?)Three patients reported facial asymmetry after BTX-A injections, two very mild. (Please correct grammar) BTX-A, 5-10 units (Please correct grammar) were injected at the contralateral sites to avoid facial asymmetry, and undesired cosmetic effects in one patient (with premaxillary pain) at subsequent injections. (Please rephrase the sentence; the essence is not clear) Two patients developed new sensations after treatment. One patient reported sharp shooting (Pain?) around (Ipsilateral or contralateral or both) nostril and eye after three months, and another patient experienced pins and needles sensations radiating to nostril and eyes for two days after injection. There was no significant adverse effects reported from long term BTX-A therapy. (Is this a conclusionary statement?)~~

Three patients reported transient partial hemi facial paralysis after BTX-A injections. 5-10 units of BTX-A were injected at the contralateral site to address the undesired cosmetic adverse effect and 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 three months, and another patient experienced pins and needles sensations radiating to the ipsilateral nostril and eyes for

two days after injection. None of the patients reported experiencing any serious adverse effects from long-term BTX-A therapy.

Discussion

The International Association for the Study of Pain (IASP) defines neuropathic pain as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [47]. ~~ICOP clarifies the diagnosis of PTNP and differentiates it from persistent dentoalveolar pain (PDAP), which is idiopathic and primary in nature and not secondary to surgery[5]. Post-traumatic trigeminal neuropathic pain (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 like such as anaesthesia, to mild or severe pain over the injured dermatome distribution [6]. Treatment of neuropathic pain is problematic (Improve language) as it various responds to psychological, medical, and alternative methods. (Please correct grammar) There were various medications recommended by international guidelines [16 19,23], including tricyclic antidepressants [17] and gabapentanoids, which also have a high number needed to treat (NNTs) (pregabalin: 7.7; gabapentin 6.3) [16]. The high gabapentanoids NNTs between four to eight, (Please correct grammar and punctuations) which provides a 50% pain relief response, are far from ideal [48] with high comorbidity and drug intolerance [19].~~ Persistent dentoalveolar pain (PDAP), which was previously thought to be PTNP, was excluded from the 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. 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 anaesthesia to mild or severe dysaesthesia over the injured dermatome distribution[2]. The burdens in managing chronic PTNP patients were their inconsistent pharmacotherapy response, poor drug tolerance and high gabapentanoids drug number-to-treat (pregabalin: 7.7; gabapentin 6.3)[17].

~~The burden in managing patients with chronic (Suggest: PTNP) post-traumatic neuropathic pain patients with poor pharmacotherapy outcomes (Please rephrase and correct grammar) may further place a clinician in dilemma and difficult treatment decisions. A diagnostic peripheral nerve block (PNB) may be helpful to determine a patient's response favourably(Please correct grammar) to BTX-A therapy. However, there is little evidence for orofacial pain diagnostic PNBs to prove their diagnostic capability [49]. (Please rephrase and correct grammar; the essence is lost) Of course, one has to phenotype the pain [6,7] precisely, with correct diagnosis[50], and the patient appropriately endotype (Please explain what endotype means?) to ensure optimal pain management [51]. Patients' (Please correct grammar) compliance with pain medication for neuropathic pain are (Please correct grammar) poor, with less than 45% of patients continuing their treatment [52]. Inadequate response to medication may be due to lack of motivation to take medications as preferring a quick fix to their problem [53,54], medication intolerance which is likely psychosomatic [55], and medication sensitivity both preventing the patient from achieving optimal dosage to manage their pain without side effects [56-58]. Thus, a holistic assessment is essential to identify possible psychological factors that will impact patients' compliance (Please correct grammar) with medication.~~

~~The mechanism of neuropathic pain is complex and involves peripheral and central nervous systems, and key interactions within sensory pathways have been discovered, but no common molecular mechanism leading to neuropathic pain has only been recently identified [59,60]. An overview of the pathophysiology of trigeminal PTNP has been recently published [61]. There is recognition that patient vulnerability is a crucial issue, reinforcing the need for holistic assessment and management [62]. It is a debilitating condition that significantly affects the patients' quality of health, leading to psychosocial dysfunction and poor oral or dental health. (Please correct grammar)~~

~~Therapeutic peripheral nerve block (PNB) deliberate interrupts (Please correct grammar; what does this mean?) an action potential (both transduction and/or transmission) for pain relief and is generally applied to a specific peripheral sensory nerve. There is little evidence supporting the screening of patients using local anaesthetic diagnostic blocks or regional nerve blockade. (Please correct vocabulary~~

and grammar) Botulinum toxin A (BTX) is recommended for therapeutic PNBs. However, it is recommended that BTX is used peripherally, sub-dermally, or submucosally without local anaesthetic with adrenaline to maximise uptake of the toxin to nerve cell bodies and synapses [63]. The antinociceptive effect of BTX is hypothesised to be related to its ability to inhibit the release of noncholinergic neurotransmitters and nociceptive mediators such as substance P, calcitonin gene-related protein (CGRP) and the expression of transient receptor potential vanilloid 1(TRPV1), which are associated with neurogenic inflammation and peripheral sensitisation [39,64,65] at the local site. As nerve injury expresses the release of those neurotransmitters, (Please correct grammar) BTX might be considered a therapeutic agent used as a peripheral nerve block (PNB) against chronic neuropathic pain [66]. The suppressive effects of BTX on the trigeminal nociceptive system were demonstrated in a study in which BTX could inhibit pain conduction after intradermal injection of capsaicin in the forehead [67]. This suggests a local peripheral effect of BTX on the cutaneous nociceptors [67]. In addition, an in-vivo study on the rat's (Please correct grammar) trigeminal ganglion has shown the antinociceptive role of BTX retrograde axonal transport from the primary periphery site to the central nervous system [68].

The safety and efficacy of repeated BTX-A injections have been reported in peripheral neuropathic pain[24]. Attal N et al. conducted a placebo-controlled randomised control trial of 68 patients with peripheral neuropathic pain (not restricted to PTNP) and has published promising results on the efficacy and safety of repeated BTX-A injections [24]. (Please follow the journal's citation style; avoid doubling citations) Almost two-thirds of the BTX assigned group was post-traumatic or post-surgical neuropathic pain. (Please correct grammar) Unfortunately, the improvement was not significant after the first BTX-A injection compared to the placebo injection group. However, they achieved a significant improvement in pain intensity at six months, after the second injection, compared to the placebo group (adjusted effect estimate −0·77; 95% CI −0·95 to −0·59; p<0·0001). Therefore, they concluded that the accumulative (cumulative?) chemo-denervation effect of repeated BTX-A injections cycles is superior against peripheral neuropathic pain to a single injection. (Please correct grammar) The only side-effects noted were was severe pain during BTX-A injection, but there was no significant difference with the placebo group (p=1.0), and concluded the safety of BTX-A injections [24]. BTX-A is now recommended

to treat focal neuropathic pain [16]. Attal et al. reported that sensory changes such as mechanical allodynia and limited thermal deficit ($p<0.05$) were valuable predictors in stratifying patients' positive response to BTX-A [24]. (Please correct grammar) A more recent study of patients with neuropathic pain of different causalities could be stratified into three groups, pinprick pain (paraesthesia), deep pain and elicited mechanical allodynia. (Please correct grammar and rephrase the sentence) The latter groups (which groups are the authors describing?) responded well to BTX-A injections but not the paraesthesia group [69].

BTX-A has been proven to be effective in trigeminal neuropathic pain. A systematic review, which included four prospective randomised controlled studies assessing the efficacy of BTX-A in trigeminal neuralgia, reported that 70 to 100% of patients reported improvement in pain after the injection [70]. Patients receiving botulinum toxin A for trigeminal neuralgia had higher odds of achieving a more than 50% reduction in pain scores [71,72]. A recent meta-analysis of four randomised control trials (RCTs) (42-45) including 178 patients (BTX-A: n=99; placebo: n=79) revealed a significant superiority of BTX-A in reducing pain score (RR 2.87, $p < 0.0001$) and frequency of attacks ($p < 0.0001$), documenting a benefit duration up to three months and mild to moderate and self-limiting adverse events [73]. To sum up, BTX-A may represent a valuable therapeutic tool in the clinical management of TN by injecting BTX-A in the trigger's zones [74,75]. The first clinical effect of BTX-A appears at its peak after two weeks and is reduced at four weeks after treatment. The effect of BTX-A last for three to six months and can up to seven to nine months with repeated injection [70].

An open-label study supported the potential value of administrating BTX-A in patients diagnosed with refractory PTNP and not responding to routine systemic and local antinociceptive agents that showed significant pain relief post six months BTX-A treatment in all 15 patients diagnosed with drug-refractory trigeminal neuralgia ($p<0.001$) [31]. (Please split the sentences; they hardly make sense as a collection; please clarify: are the authors referring to PTNP or refractory TN here?) A similar outcome is seen in the increased effectiveness of BTX-A induced analgesia with repeated injection in PTNP [42-46] (Please correct grammar) compared to BTX-A in other peripheral neuropathic pain diseases. PTNP

patients often presented with mechanical and thermal hypersensitivity, and this phenotype has a better response to BTX-A treatment [24,69].

There is no consensus (Suggest: We could not find a consensus) on the therapeutic dosing range of BTX-A to achieve a good therapeutic effect with reducing adverse effects. The dose varies and is dependant on clinician's choice and the patient's subjective pain score during the review visits and experience. The total dosage of BTX-A used in our clinical practice (mean: 25 units and total maximum dose: 50 units) was comparable with the five case reports in the literature review. Repeated regular BTX-A injections have been shown to be safe, increasing therapeutic benefits, and sustained continuous reduction in pain score. This sustained pain relief from repetitive BTX-A injection is reflected in two of our patients with a follow up of three and five years, respectively [42,45]. Prolonged BTX-A administration will (Suggest: may) increase the duration of response, and patients may need a less frequent and high concentration of BTX-A [76]. (Please comment on the fact that repeated administration of BTX-A may actually reduce efficacy due to the antigenic nature of the toxin) Nevertheless, the repetitive dosage or frequency (time gap between injections) of BTX-A should be reduced once a significant pain relief was achieved, as seen in the use of headache or migraine, to reduce the long-term possibility of untoward BTX-A adverse effects. (Please enumerate the adverse effects)

Long term use of BTX-A may develop patients' tolerance towards BTX-A and subsequently lose its antinociceptive sensory effect [77]. A practice of minimum effective antinociceptive BTX-A concentration should be administered, and the frequency of booster injections should be minimiszed with an interval of at least three months. The patient should be warned of the possible migration of BTX-A, which may affect the patient's facial symmetry and muscle functions. There was insufficient documentation on BTX-A induced muscle atrophy's adverse effect (Please correct grammar) in chronic repetitive botulinum toxin cycle injection [78]. Salari M et al. have suggested factors contributing to BTX-A induced muscle atrophy, such as type of BTX-A, advanced age, gender, obesity, muscle reinnervation and characteristic, underlying comorbidities, muscle spindles, blood perfusion, and fats [78]. (Please correct grammar)

~~The primary cause of PTNP is often associated with dental procedures (Avoid multiple repetitions of the same sentence) BTX-A has been injected submucosal intraorally (Please correct grammar) over the pain or trigger zone along with the distribution of the maxillary and inferior alveolar nerve branches. Similar successful analgesic effectiveness and pain relief pattern were achieved with submucosal intraoral BTX-A injection as to subcutaneous injection as reported in our case series and literature review [42,44-46]. The intraoral BTX-A injection has a latency period of one to two weeks following the injection [41,42,43,46] except for one study which Cuadrado M et al. reported a three-day latency period [45] for the BTX-A analgesic effect. (Please correct grammar) The duration of the analgesic of BTX-A (Please correct grammar) lasted for two to five months [41,42,44-46]. Repeated cycles of three monthly (Please correct grammar) intraoral injection prolong the BTX-A analgesic effect with a higher percentage of pain relief (70%) [41,42,45]. The side effect is minimal, with the most common transient facial asymmetry (Please correct grammar) mainly due to unilateral application of the drug. A contralateral BTX-A injection could be offered to the patient to reduce the cosmetic facial asymmetry. (Citation needed) Reports of mucosa dryness were reported (Please correct grammar) in intraoral submucosal injection for persistent dentoalveolar pain, but no soft tissue abnormality or lesion was observed [41]. The dosage involved is within 10 to 50 units [41,42,44-46], with one randomised controlled trial study noted a similar effect on a low dosage of 25 units a high dosage of 75 units [79]. (Please correct grammar)~~

~~The submucosal intraoral injection is safe and easy injected (Please correct grammar) in the buccal vestibules, gingiva and hard palate. However, caution that (Please correct grammar) it should not be injected in vital structures innervated by the motor nerve and have rich blood circulation, (Please correct grammar) such as the tongue, floor of the mouth and soft palate. This may lead to fatal events such as airway compromise, swallowing, speech (Please correct grammar and reword the sentence) and systemic nervous toxicity. The presence of a vasoconstrictor could help localisze the effect of BTX-A with limited diffusion of BTX-A to distant regions from the injection site and reduce pain during injection. Nonetheless, it may reduce the analgesic efficacy and distribution, and multiple injections sites may be needed as the pain or trigger zones are often not localiszed to a single point of the traumatic nerve dermatome innervation. As there is no reported sensory numbness or significant injuries to the~~

~~oral mucosa, post BTX-A injection, BTX-A could be used without a vasoconstrictor to increase its analgesic effect. A minimal dose of BTX-A could be injected on the contralateral non-painful site to prevent cosmetic facial asymmetry. (Repetition)~~

~~Our clinical experience and published case reports showed (Please correct grammar) that BTX-A has significantly impacted the patient's pain and enhanced the quality of the patient's mental and physical health. BTX-A could be used in refractory neuropathic pain patients (Please correct grammar: please avoid laymen language) with no improvement or intolerance towards the drugs' side effects. (Please correct grammar) Polypharmacy in a patient could be avoided, reducing the risk of adverse drug reactions such as falls and cognitive impairment, drug interactions, drugs to disease interaction, and poor patient's compliance (Please correct grammar) to medications. The major caveat is that the use of BTX-A in chronic neuropathic orofacial pain is 'off label'. Patient selection is an important aspect. Despite the wide application of BTX-A in the orofacial region, the evidence for BTX-A as a therapeutic PNB for PTNP is lacking. Unfortunately, there are no high-quality studies on peripheral neuropathic pain secondary to trauma to date. 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, randomised clinical trials. BTX-A as PNBs to treat PTNP findings are encouraging, but high-quality evidence is not available to conclude that BTX-A injections can become a standardiszed treatment for refractory PTNP. A large controlled randomised clinical trial is essential to establish the efficacy of BTX-A in providing immediate and sustainable pain relief with consensus guidelines on the therapeutic dosing range, total doses and limits and treatment algorithms. (Please correct grammar)~~

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 been recently published[50].

The suppressive action of BTX-A on the trigeminal nociceptive system was demonstrated in a study in which BTX-A inhibit pain conduction after intradermal injection of capsaicin in the forehead[51]. In

addition, an in-vivo study on the rat's trigeminal ganglion has shown the anti-nociceptive 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 anti-nociceptive effect of BTX-A is hypothesised to be related to its ability to inhibit the release of noncholinergic neurotransmitters and nociceptive mediators such as substance P, calcitonin gene-related protein (CGRP) and the expression of transient receptor potential vanilloid-1(TRPV1), which are associated with neurogenic inflammation and peripheral sensitisation[54-56] at the injured site. This inhibits the transmission of nociceptive impulse from the primary periphery 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 fibres[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, we administered a mixture of BTX-A and local anaesthetic without vasoconstriction such as adrenaline to allow a wider toxin diffusion and uptake area.

Poor patient drug compliance was reported in a study, with less than 45% of patients continuing their treatment[60]. Inadequate therapeutic response to medication may be due to a lack of motivation, such as preferring a quick fix to their problem[61,62], medication intolerance, which is likely psychosomatic[63], and medication sensitivity, which prevents the patient from achieving optimal therapeutic dosage to manage their pain without side effects[64-66]. Thus, psychological behaviour 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) the PTNP patients based on their pains' characteristics[68,69] as a responder or non-responder towards 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 a responder to BTX-A. A study on patients with neuropathic pain arising from different causalities has classified patients into three groups; pinprick pain (paraesthesia), deep pain and elicited mechanical allodynia. Patients in the deep pain or allodynia groups respond better to BTX-A therapy but not the paraesthesia group[71,] and this benefit PTNP patients as they often present with mechanical and thermal hypersensitivity[70,71]. This was reflected in our case series, where six of nine patients with a history of continuous pain or allodynia reported improvement in their pain at three months review. Hence, the importance of somatosensory assessment is suggested before a clinical decision on BTX-A administration.

A diagnostic peripheral nerve block (PNB) may be helpful to ascertain a favourable patient's response to BTX-A therapy, but limited evidence is available to support the screening of patients using local anaesthetic 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, we did not perform this in our centre.

We could not find a consensus on the therapeutic dosing range of BTX-A in achieving an ideal therapeutic result while reducing the adverse effects. The dose 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 our clinical practice was comparable with 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 randomised control trial of 68 patients with peripheral neuropathic pain (not restricted to but two-thirds of the patients 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. However, the pain intensity significantly

improved six months after the second injection compared to the placebo group ($p<0{\cdot}0001$). Repeated regular BTX-A injections in neuropathic pain have been shown to be safe while increasing the therapeutic benefits of BTX-A[42,45]. The sustained pain relief effect derived from repetitive BTX-A injection was reflected in two case series patients with a follow-up of three and five years, respectively. Prolonged BTX-A therapy may increase the duration of analgesia response, and patients may need a less frequent BTX-A administration and a lower BTX-A concentration[73]. The accumulative chemo-denervation effect of BTX-A injections was superior to single used against peripheral neuropathic pain[42,70]. The only unpleasant event noted in our case series was pain during BTX-A injection, but studies have shown no significant difference in pain during injection between the placebo and treatment group ($p=1.0$)[70]. However, long-term use of BTX-A may develop patients' tolerance toward BTX-A and subsequently lose its anti-nociceptive sensory effect[74]. To avoid the long-term possibility of untoward BTX-A adverse events and development of sensitisation towards BTX-A in its treatment for headache and migraine, administration of minimum effective anti-nociceptive BTX-A dosage and minimising the frequency of booster injections with an interval of at least three months or more once achieving constant pain relief were practised[38].

The use of BTX-A has been viewed as safe with a low risk of severe adverse events if a thorough patient's medical history was obtained and the practice of appropriate dosage and injection technique. The side effects of BTX-A could be classified into transient, well localised, and reversible complications and potentially serious systemic botulism events[75]. Common transient BTX-A side effects could occur immediately or days after treatment, including pain, oedema, erythema, ecchymosis and hypoaesthesia[75]. Concerned of botulism in the orofacial region is the risk of dysphagia, dysphonia, diplopia, breathing difficulties, and anaphylactic allergic reaction over BTX-A. This is reflected in our case series, with no patients having any permanent loss of oro-facial muscle function and systemic toxicity on repeated use of BTX-A. It is advised to caution the patient of the possible broader area migration of toxin from the injection site, which may cause localised transient facial muscle paralysis. There was insufficient documentation on BTX-A-induced muscle atrophy's adverse effect 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, obesity, muscle reinnervation and characteristic, underlying comorbidities, muscle spindles, blood perfusion, and fat volumes[76]. It has been hypothesised that systemic adverse effects could occur due to accidental intravenous injection of BTX-A[77] or retrograde transport of the toxin to the nerve cells' bodies[78].

The submucosal intraoral injection is safe and simple to be delivered in the buccal vestibule, gingiva and hard palate as practised in our centre. The side effects were minimal, with the most common transient cosmetic facial asymmetry reported in the case series and literature mainly due to the unilateral application of the drug. A contralateral BTX-A injection[79] or injection of BTX-A into facial muscles that antagonise the affected muscles[75] could be offered to the patient to address the issue. Improper intraoral injection technique may lead to BTX-A diffusion to adjacent salivary glands and causes xerostomia, which has been reported in 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 nervous toxicity events. The use of a vasoconstrictor could help localise the effect of BTX-A by limiting the diffusion of BTX-A to adjacent vital structures. Nonetheless, it may 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 localised to a single point of the traumatic nerve dermatome innervation.

As reported in our case series and literature, the combined submucosal and subcutaneous BTX-A injections have been effectively treated intraoral PTNP[42,44-46]. Submucosal BTX-A injection over the pain or trigger zone concerning the injured distribution and innervation of the maxillary or mandibular branches of the trigeminal nerve has displayed a similar analgesic latency period as per subcutaneous administration, between one and two weeks after BTX-A injection[41,42,43,46] except one study reported a three-day latency period[45]. The BTX-A analgesic effects were reported to continue for two to five months[41,42,44,45,46]. Studies reported that repeated three-monthly intraoral BTX-A injection cycles 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 reported case series falls between the literature's reported submucosal BTX-A injection dosage, between 10 and 50 units[41,42,44-46].

Based on the retrospective case series and literature review, the use of BTX-A in refractory PTNP patients has greatly improved patients' pain control and enhanced the patients' 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 to treat PTNP are encouraging, but there is no high-quality evidence to conclude that BTX-A injections can become a standardised 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, randomised clinical trials. In addition, patient profiling and selection are crucial to be assessed before BTX-A treatment.

Conclusion

~~Although the quality and evidence level of the published literature was low, the positive correlation (Are you talking about statistical correlation) on the use of Onabotulinum toxin A (BTX-A) to treat refractory post-traumatic trigeminal neuropathic pain (PTNP) that failed to respond to first line pharmacotherapy is compelling. We have provided initial evidence that BTX-A may be an adjuvant treatment option for patients suffering from neuropathic pain with a peripheral component presenting intraorally and involving the dentoalveolar areas. In most cases, submucosal intraoral BTX-A injections are well tolerated and a valid and safe treatment against refractory PTNP with no identified permanent unbearable adverse effects. The relative safety profile of BTX-A allows repetitive BTX-A injections cycles (Please correct grammar), producing sustainable pain relief in patients and improving patients' (Please correct grammar) quality of life and health. However, these findings should be interpreted cautiously~~ Although the quality and evidence level of the published literature was low, the benefits of BTX-A to treat refractory PTNP are compelling. We have provided our experience on the benefit of BTX-A 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 repetitive BTX-A injection to achieve continuous pain relief, which will inadvertently improve patients' psychosocial function. However, these findings should be interpreted cautiously due to the poor evidence quality.~~.~~ A large-scale randomised control trial is suggested to ~~be conducted to~~ assess BTX-A's safety and effectiveness as an anti-nociceptive agent in treating painful refractory PTNP. A regulated guideline on using~~the use of~~ BTX-A in ~~clinical practice in~~ managing PTNP is essential to achieve the best effect while minimising any unknown long term BTX-A adverse effect.

Highlights

Key Findings

- Botulinum toxin may be a novel interventional treatment for refractory post-traumatic trigeminal neuropathy.
- ~~Botulinum toxin injection is relatively safe to be repetitively used in the long-term management of neuropathic pain in patients with post-traumatic trigeminal neuropathic pain.~~
- ~~The use of botulinum toxin could replace the need for polypharmacy in managing neuropathic pain symptoms.~~ The potential use of botulinum toxin as an adjunct therapy may reduce the need for polypharmacy in managing neuropathic pain symptoms.
- Large and well-designed randomised controlled clinical trials are needed to support botulinum toxin injection as a relatively safe repetitively therapy in the long-term management of patients with ~~therapy for~~ chronic post-traumatic neuropathic pain.

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