Original Article

Single-Dose Botulinum Toxin as Adjunctive Treatment for Trigeminal Neuralgia: A Pilot Study

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***Objective*:** To evaluate the efficacy and safety of a single dosage of botulinum toxin type A (BTX-A) injection as an add-on therapy in patients suffering from trigeminal neuralgia (TN).

Materials and Methods: Thirteen classical TN patients were enrolled in a 7-week long prospective open-label pilot study. A single dosage of BTX-A (25 U/1.5 mL) injection was extra orally and intradermally administered into the skin of the trigger area of TN pain. The primary outcome measures were pain severity per day, assessed by numeric rating scale (NRS), pain attack frequency and number of antiepileptic medications taken per day.

Results: A total of 8 patients (1 man and 7 women) completed the study and were all improved regarding severity and frequency of pain attack. The Wilcoxon signed-rank test showed a significant difference in frequency of pain attack before injection and at 4 weeks and 6 weeks after injection ($p<0.05$). Paired t-test of pain severity showed significant difference ($p<0.05$) between severity of pain before and after injection. Wilcoxon signed-rank test showed significant reduction in medication intake in all patients up to the end of trial at 6 weeks follow-up ($p<0.05$). In one patient, pain was completely eradicated and there was no need for further medication. BTX-A was generally well tolerated and there were no serious treatment-related adverse events.

Conclusion: The present study revealed a clinical benefit in efficacy and safety of the combination of single dosing of BTX-A and pharmacotherapy for patients with TN.

***Keywords*:** Trigeminal neuralgia, Botulinum toxin, Carbamazepine, Pain severity, Pain frequency

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Trigeminal neuralgia (TN) is a characteristic pain in the distribution of one or more branches of the fifth cranial nerve. The pain is intermittent, abrupt in onset and termination, triggered by stimuli that normally do not cause nociceptive responses, and often described as electric shock-like, sharp shooting or stabbing pain[1]. However, some patients may report continuous burning pain between these paroxysmal attacks[2]. TN is usually chronic with the manifestation of the severe and remission period of pain and it is estimated that approximately 4 to 28.8/100,000 people globally suffer from this condition with elderly female groups among the most affected[3,4]. Although, the etiology of the TN is not fully understood, it is suggested that the symptom is the result of nerve injury that was caused by neurovascular compression of the trigeminal nerve in the root entry zone from the adjacent blood vessels or caused by a tumor or cyst at the cerebellopontine angle or multiple sclerosis[5] causing ephaptic cross-talk between fibers mediating light touch and those involved in pain generation[6].

Similar to the other neuropathic pain condition, TN frequently causes major suffering and disability among patients and their care givers. The most recent guideline by both the European Societies of Neurological Societies and the American Academy of Neurology recommended carbamazepine (CBZ) and oxcarbazepine (OXC) to be offered as first-line treatment for the management of TN pain[7]. However, CBZ and OXC are associated with several side effects, such as dizziness, lack of fatigue, nausea, vomiting, occasional induced leukopenia, hyponatremia and toxic hepatitis[8]. The higher incidence of severe skin adverse reaction from CBZ and OXC found in Asian patients make

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medical management for this condition challenging[9,10]. Even in patients in long-term use who could tolerate side effects of CBZ/OXC well, up to 50% of them becomes refractory to drug therapy[11]. Neurosurgical treatment using microvascular decompression (MVD) surgery is therefore recommended for the treatment in patients who developed drug allergies, intolerable side effects or inadequate pain control from medications[12]. but it may not be suitable in the elderly group of patients and up to 30% of post-surgical cases may develop recurrence of TN within 24 months after MVD surgery; long-term antiepileptic treatment is required[13].

Botulinum toxin type A (BTX-A), a potent neurotoxin produced by gram-positive bacterium *Clostridium botulinum*, blocks acetylcholine release from neuromuscular junction resulting in muscle relaxation. BTX-A is a drug of choice for several medical conditions such as dystonia, blepharospasm, hemifacial spasm, migraine or other muscle movement disorders and headaches[14,15]. However, it has recently been used to treat various type of neuropathic pain conditions including trigeminal and postherpetic neuralgia[16]. Several animal studies have suggested antineuralgic mechanisms of BTX-A by blocking the release of calcitonin gen-related peptide from sensory neurons and it may deactivate sodium channels in central nervous system neurons[17,18]. Based on the current evidence from systematic review and meta-analysis, it is concluded that BTX-A maybe effective and relatively safe option for the treatment of TN, however, the trials included in the systematic review were differ in the diagnostic criteria used for the recruitment of TN patients[19]. In addition to the TN diagnostic criteria used in the previous studies, volumes of injected BTX-A, routes of injection, injection frequencies, and injection sites have varied among studies. As little as 25U of BTX-A was administered according to Zhang et al[20] compared with a maximum of 100U given by Shehata and colleagues[21]. However, no significant difference was found in comparing the antineuralgic efficacy between low dosages (25U) and high dosages(75U) of BTX-A over 8-week follow-up period[20]. The results of the study by Zhang and co-workers showed that repeated dosing of BTX-A did not contribute to improved clinical outcome in TN patients[22]. The objective of our study was therefore to assess the efficacy and safety of single and low dosage of BTX-A injection as adjunctive therapy in patients with TN.

Materials and Methods

Study design

The present study was a 7-week prospective open-label clinical study of BTX-A as an add-on therapy in the management of patients with TN. The study protocol was reviewed and approved by the local ethics committee in human research of Khon Kaen University (number HE591208). The study details including all possible adverse reactions from BTX-A were explained to each patient and written informed consent was obtained before being enrolled into the study. Patients were free to discontinue from the study at any time and escape medication for pain using other antiepileptic medications were given to patients if needed. The overall duration of the study for each patient was 7 weeks, including a 1-week observation period to establish baseline pain symptoms, followed by a 6-week study period with follow-up visits were conducted at week 1, 2, 4 and 6 after a single BTX-A injection.

Study participants

Eligible patients were recruited from the Orofacial Pain Clinic, Faculty of Dentistry, Khon Kaen University between June 2016 to October 2017. The inclusion criteria included: non-pregnant patients (>20 years) who were diagnosed with classical TN according to the classification of International Headache Society (ICHD-II)[23] and without structural pathology at the base of skull as shown in CT or MRI of the brainstem, patient's baseline pain severity with their usual medication: CBZ or OXC exceeded four out of 10 on the categorical numerical rating scale (NRS) were included, and patients who were failure of recent treatment, either from inadequate pain control or had developed unwanted or intolerable side effects. At baseline, patients were prescribed CBZ or OXC to alleviate their pains and these medications remained unchanged and no new medication was added throughout the course of the study. Exclusion criteria were those who had facial skin infection at the injection site or had conditions that put them into greater risks when injected with BTX-A. Patients with significant unstable medical conditions including mental illnesses and impaired cognitive functions were excluded from the study.

Baseline data were recorded 1 week before BTX-A injection; the severity of pain per day, the frequency of pain attack per day, and the amount of CBZ or OXC taken per day. The injection sites selected in the present study were perceived pain and trigger zones as shown in Figure 1. In the present study, the volume of injected BTX-A was 25U, delivered through intradermal routes.

Outcome measures

Thirty minutes before bedtime each night, patients were required to record daily pain diary. The daily diary recorded include average daily pain severity score measured according to an 11-point numeric rating scale; NRS, average number of pain attack per day, number of tablets of CBZ or OXC taken and adverse reactions experienced in the previous 24 hours. At each follow-up visit, the following items were assessed; pain severity and pain attack frequency from baseline to endpoint, self-evaluation of global assessment of patient satisfaction according to five-point scale (1, much worse; 2, minimally worse; 3, no change; 4, minimally improved; 5, much improved). Safety was measured as the occurrence of adverse events and record with information including the date of onset, severity, duration, frequency, treatment required (if any), relationship to BTX-A injection, and outcome.

Statistical analysis

Pre-treatment data were compared with the post-

treatment phase, with the average daily pain severity, the daily number of pain attacks and number of tablets of medication taken daily were analyzed and compared at 1-week before and 1-week, 2-week, 4-week and 6-week after BTX-A injection. If obeying normal distribution, data were assessed using mean ± SD and intra-group comparisons were evaluated by means of paired t-test. If not, data were assessed using median values and the Wilcoxon signed-rank test was used. Standard software package (SPSS v20.0; SPSS Inc. (IBM), Chicago, IL, USA) was used for statistical analysis, setting significance at $p<0.05$.

Results

A total of 13 patients were recruited in the present study but not all completed. Five patients withdrew from the study pre-maturely before completing the study and are therefore not included in the analysis. Two patients withdrew from the study because of health issues; one patient was diagnosed with liver problem and the other from hemorrhagic stroke. Three patients withdrew for social reasons. Their ages at entry ranged from 49 to 79 years (the mean age being 67.25±8.48) and the pain was localized on the left in 2 patients, on the right in 6 patients. The second division of trigeminal nerve was involved in 2 patients and in 6 patients was suffering from the third division of trigeminal nerve pain. The average duration of the disease before BTX-A injection was 73.69 months (SD ±91.03). Seven patients had previously tried CBZ and one had tried OXC and during the study all medication's prescription remained unchanged.

The results of the mean pain severity score (mean NRS recorded daily) for 8 patients after BTX-A injection dropped sharply from 6.25 before the injection to 3.00 at 1-week follow- up and then slowly decreased to 2.87, 2.12 and 1.38 at 2-week, 4-week and 6-week follow-up, respectively (Figure 2). A similar tendency toward the reduction of number of pain frequency (the mean times per day) at 1 week after BTX-A injection. The mean frequency of pain attack dropped markedly and then gradually reduced on the 2-week, 4-week and 6-week follow-up visits to 3.64, 3.52, 3.16 and 3.03 times, respectively (Figure 3). Furthermore, the average number in tablets of drugs taken of patients after the injection was 0.96, 0.92, 0.91 and 0.89tablets per day, respectively. From the Figure 4, the numbers were clearly decreased from 1 week to 6 weeks after injection.

For the comparison of the average pain severity using NRS when the values at the beginning of the study were compared with week 1 ($p = 0.01$), week 2, ($p = 0.02$), week 4 ($p = 0.01$), and week 6 after BTX-A injection ($p = 0.01$), the differences turned out to be of statistically significance. Likewise, for the comparison between week 1 and week 6 after the injection, the results were statistically significant (Table 2).

For the comparison of the average frequency of pain attack (times per day) at baseline versus the first week ($p = 0.12$), at baseline versus the second week ($p = 0.08$), the results were not statistically significant within the first two weeks. However, when the pain frequency was compared at baseline versus 4 weeks ($p = 0.03$) and 6 weeks ($p = 0.03$), the results were of statistical significance. Similarly, the comparison between the stages (week 1 and week 6) yielded significant results ($p = 0.03$) (Table 3).

From the comparison of the mean of the numbers of medication taken (tablets per day) at baseline versus week 1, 2, 4 and 6 week after BTX-A injection, there were statistically significant differences ($p<0.05$) between

Figure 1. Botulinum toxin injection site at the trigger area of volunteers.

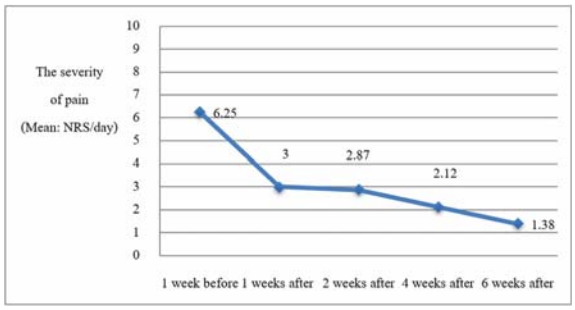

Figure 2. The mean of the severity of pain before and after Botulinum toxin injection.

Table 1. The levels of the satisfaction before and after BTX-A injection

Levels of the satisfaction	Before injection: n (percentage)	After injection: n (percentage)			
		1 week	2 weeks	4 weeks	6 weeks
Not satisfied	1 (12.5)	1 (12.5)	0 (0)	0 (0)	0 (0)
Slightly satisfied	0 (0)	1 (12.5)	0 (0)	0 (0)	0 (0)
Modertely satisfied	2 (25)	1 (12.5)	3 (37.5)	2 (25)	2 (25)
Very satisfied	3 (37.5)	2 (25)	2 (25)	3 (37.5)	2 (25)
Extremely satisfied	2 (25)	3 (37.5)	3 (37.5)	3 (37.5)	4 (50)

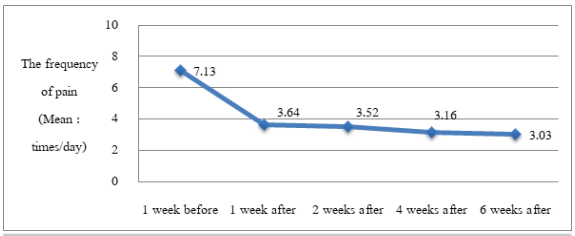

Figure 3. The mean of the frequency of pain before and after BTX-A injection.

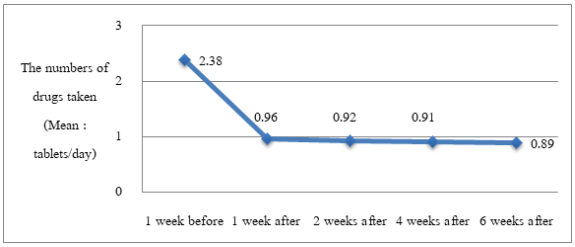

Figure 4. The mean of the number of drugs taken be fore and after BTX-A injection.

number of tablets taken before injection (2.38±0.74) and the following visits (0.96±1.28, 0.92±0.99, 0.91±0.98, 0.89±0.94, respectively) as shown in Table 3. The initial average dose of CBZ was 476±148 mg before being enrolled in the trial, and at 6 weeks after BTX-A injection it was 178±188 mg.

At the end of the trial, all patients rated themselves on the global evaluation scale as extremely satisfied (n = 4), very satisfied (n = 2) and moderately satisfied (n = 2) as shown in Table 1. All treatments were generally well tolerated and there were no serious treatment-related adverse events. One patient reported dizziness for 1 week and one patient reported facial asymmetry and resolved within 4 weeks after injection. We did not have any cases of dysphagia or any systemic side effects.

Discussion

Trigeminal neuralgia is a chronic and severe neuropathic orofacial facial pain with antiepileptic medications; CBZ and OXC are being recommended as first-line treatment. However, these medications need to be slowly titrated and require daily dosage administration in newly diagnosed cases, still some patients reported intolerable side effects or inadequate efficacy. Neurosurgical intervention including microvascular decompression surgery is normally recommended in refractory cases, but some complications associated with this intracranial surgery limits the application of this technique[12]. Newer and safer medication is therefore needed to manage this painful condition, particularly in the group of aging or those who developed unwanted adverse reactions. BTX-A has repeatedly shown its efficacy and safety for the treatment of TN in several clinical trials include in the systematic review[19] but there still is uncertainty as to how BTX-A should be administered, and which patients are best suited for this treatment.

In our open label, single-dose pilot study, patients receiving low dose of BTX-A injection over the area of trigger zone of sharp shooting pain. Our results showed that, with the use of low dose of BTX-A (25 U), the pain severity and attack frequency showed statistically and clinically significant improvement at each follow-up. These findings were confirmed by the studies by Wu et al[24] and Piovesan et al[25] in both studies the pain severity and attacks were considerably alleviated. The average pain severity in our study was significantly dropped from 1 to 6 weeks after BTX-A injection (p<0.05) and our findings was also confirmed by the study by Zuniga et al, which found that the severity of pain had significantly decreased after 2 weeks of injection[26]. Furthermore, the study by Turk et al also reported similar findings that the pain severity was significantly reduced within just 1 week after the injection[27]. Peak effect of BTX-A was reached about 7 to 10 days in 7 patients after injection and this finding was also confirmed by several previous clinical BTX-A study in TN, atypical odontalgia and trigeminal neuropathic pain patients[26-28].

Our result showed that the average pain attack frequency was not significantly decreased until the second week after BTX-A injection. Our results on pain attack frequency is in contrast with the study by Wu et al that reported the pain frequency was significantly decreased much faster, within just 1 week after BTX-A injection[24]. Possible explanations for this discordance could be the different treatment methods or of the exacerbation of the effects of BTX-A due to the lack of a control group. Our findings also demonstrate the beneficial of BTX-A when use as an

Table 2. The comparison of the mean of the severity of pain, the frequency of pain and number of drugs taken before and after BTX-A injection

Variables	Visits	Mean ± SD	*p*-value
The severity of pain	1 week before injection	6.25±2.12	
(mean NAS/day)	1 week after injection	3.00±1.51	0.01[a]
	1 week before injection	6.25±2.12	
	2 weeks after injection	2.87±2 .35	0.02[a]
	1 week before injection	6.25±2.12	
	4 weeks after injection	2.12±2.10	0.01[a]
	1 week before injection	6.25±2.12	
	6 weeks after injection	1.38±1.77	0.02[b]
	1 week after injection	3.00±1.51	
	6 weeks after injection	1.38±1.77	0.04[b]
The frequency of pain	1 week before injection	7.13±7.12	
(mean times/day)	1 week after injection	3.64±4.79	0.12[b]
	1 week before injection	7.13±7.12	
	2 weeks after injection	3.52±4.88	0.08[b]
	1 week before injection	7.13±7.12	
	4 weeks after injection	3.16±4.92	0.03[b]
	1 week before injection	7.13±7.12	
	6 weeks after injection	3.03±4.95	0.03[b]
	1 week after injection	3.64±4.79	
	6 weeks after injection	3.03±4.95	0.03[b]
The number of drugs taken	1 week before injection	2.38±0.74	
(mean tablets/day)	1 week after injection	0.96±1.28	0.03[b]
	1 week before injection	2.38±0.74	
	2 weeks after injection	0.92±0.99	0.04[b]
	1 week before injection	2.38±0.74	
	4 weeks after injection	0.91±0.98	0.02[b]
	1 week before injection	2.38±0.74	
	6 weeks after injection	0.89±0.94	0.02[b]
	1 week after injection	0.96±1.28	
	6 weeks after injection	0.89±0.94	0.02[b]

[a] Paired t-test, [b] Wilcoxon signed-ranks test

adjunctive therapy for TN resulting in the reduction of drugs taken which is also confirmed by the study conducted by Pioves an and colleagues that reported after BTX-A, four patients became medication free, while the others reduced their consumption by more than 50%[25].

Although the mechanism via which BTX-A exercises an analgesic effect is not completely understood, it is suggested from the animal model of neuropathic pain, that the toxin deactivates the sodium channel and changes the sodium current of a neuronal excitable membrane. Moreover, BTX-A degrades the SNAP-25 protein, which is a type of protein necessary for the exocytosis of certain neurotransmitters in the terminal axon resulting the blockage of nociceptive neuropeptides and neurotransmitters, which leads to a reduction of the peripheral pain sensitization[29]. Additionally, Fan et al demonstrates the antinociceptive mechanism of BTX-A by reducing TRPV1 expression by inhibiting plasma membrane trafficking after intra-articular administration[30]. Since there is still no animal model for TN, more research is needed to help understand the mechanism of action of BTX-A on suppressing ectopic transmission by blocking sodium channels in TN patients.

In our study, no significant safety concerns were noted and all 13 patients tolerated the drug well, and none of them developed disturbing or permanent adverse effects. There were no reported of drug allergy after BTX-A injection but there were reversely mild side effects such as dizziness and short-term facial asymmetry reported. The adverse events observed in patients were consistent with those seen in previous clinical studies and patients generally found this complication tolerable.

The major limitation of the present study was the open-label pilot design with the lack of a placebo-controlled comparison group that may have overestimated the antineuralgic effect in patients with TN and may create bias. Another limitation of our study was a short duration of the follow-up time (6 weeks) especially in patients with TN, which is a neuropathic pain condition that episodes of natural self-remission period without any treatment, can commonly be seen, and this could result in misinterpretation of the reduction in the pain severity. Even though all TN patients recruited were examined and diagnosed by the same dentist specialized in orofacial pain management, which eliminates the intra-examiner error, selection bias was probably

happened due to the study was being done in a tertiary referral center with the majority of patients being difficult to treat and refractory to previous treatment attempts. A large and well-designed blinded and randomized controlled trial is needed to evaluate the effect of BTX-A on TN, to validate our findings and to explore whether higher doses, multiple site injection and repeated administration of BTX-A provide a more sustained effect and could possibly be used alone without additional medication in patients with TN.

Conclusion

Using botulinum injection with CBZ or OXC in patients with TN can reduce the severity of pain, the frequency of pain attack and the amount of medication taken compared to using anticonvulsant drugs alone. The authors suggest that BTX-A injections would offer some distinct advantages over existing therapies with respect to efficacy and safety for TN patients.

What is already known on this topic?

The main and first-line treatment for patients with TN is antiepileptic medication particularly carbamazepine and oxcarbazepine. Local injections of BTX-A may be an effective and safe therapeutic option for the treatment of TN. At present, there are no clinical guidelines for administration of BTX-A for TN pain. Most treatments are subcutaneous or intradermal, and BTX-A is also injected intramuscularly or into the surrounding tissues.

What this study adds?

Our preliminary results suggest that using BTX-A as additional therapy, even in low dosages has some anti-neuralgic properties and there is a marked absence of significant side effects so making the toxin a potentially useful drug in the management of TN given that most recommended epileptic medications result in significant side effects. A single-dose BTX-A injection for TN patients is an easy procedure, both in medical and dental clinical setting as it does not need complex titration regimen and is relatively safe for elderly and frail patients, compared to drugs used for the management of patients with this entity.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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