The Effects of Botulinum Toxin Type A for the Treatment of Trigeminal Neuralgia in Prasat Neurological Institute

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Abstract

Background: Trigeminal neuralgia (TN) is a neuropathic facial pain condition. Botulinum toxin type A (BTX-A) has been approved by FDA in treating chronic migraine and has been studied as a therapeutic option in various types of neuropathic pain.

Objectives: To evaluate the efficacy and safety of a BTX-A in patients with refractory TN.

Methods: In this open-label pilot clinical trial, twelve patients with refractory idiopathic or classical TN were included. All patients were received 25 units of BTX-A in painful trigger points using subcutaneous and intradermal techniques as an additional treatment, while all patients received their conventional treatment concurrently. The primary outcomes were pain severity assessed by visual analogue scales (VAS) and attack frequency per day (F). Both VAS and F were compared from baseline to eight-week endpoint. The secondary outcomes were patient' quality of life assessed by Quality of Life Scale (QoL scale) and Penn Facial Pain Score-Revised (Penn FBS-R).

Results: A total of 12 patients completed the study. Seven women and five men aged 47-80 years (median 57.5, IQR 20.5) suffering TN from 2 to 15 years (median 5.5, IQR 4.25). In primary outcomes, VAS and F were significant reduced from baseline to endpoint *(p=0.05, p=0.02)* respectively. For secondary outcomes, patient's quality of life as measured by QoL scale and Penn FBS-R were significantly improved. No systemic adverse event was noted. The reported side effect was transient facial asymmetry in one patient which automatically disappeared in 4 weeks.

Conclusion: This pilot study supports other previous studies and demonstrated that BTX-A is a minimally invasive and effective treatment for intractable TN before step up to other more invasive therapies.

Keywords: Trigeminal neuralgia, Botulinum toxin A, Efficacy, Pilot study, Treatment, Quality of life

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Background

Trigeminal neuralgia (TN) is defined by the International Headache Society (IHS) as a recurrent unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the Trigeminal nerve and triggered by innocuous stimuli.[1] TN, also known as tic douloureux, sometimes is considered to be one of the most painful afflictions in medical practice. The prevalence of TN was estimated to be 0.16 to 0.3%, equal in both male and female.[2] The second branch (alone or together with the third) of cranial nerve V was the most frequently affected.[2] According to the International Classification of Headache disorder 3rd edition (ICHD-3), TN are classified in three etiologic categories. Firstly, classical TN is caused by vascular compression of the trigeminal nerve root. Secondly, idiopathic TN was diagnosed with neither magnetic resonance imaging (MRI) nor electrophysiological tests showing significant abnormalities. Lastly, secondary TN is the consequence of other major neurologic disease such as a tumor of the cerebellopontine angle or multiple sclerosis.[1]

Based on AAN-EFNS guideline published in 2008 and current EAN guideline on trigeminal neuralgia published in 2019, the first-line treatment of TN are carbamazepine (CBZ) and oxcarbamazepine (OXC).[3,4] The evidence of efficacy for carbamazepine is stronger than oxcarbamazepine, but the latter may associated with fewer safety concerns.[3] As stated in systematic reviews and multiple RCTs, carbamazepine has shown to increase pain relief compared to placebo.[4] However, consensus expert opinion suggests that carbamazepine has a 50% failure rate for long-term (5-10 years) pain control.[5, 6] Side effects including drowsiness, dizziness, liver damage, ataxia, and has the potential for multiple drug interactions.[4] CBZ and OXC can induce serious cutaneous reactions such as Stevens-Johnson disease (SJS) and Toxic epidermal necrolysis (TEN). A strong association between HLAB*1502 and CBZ-induced SJS/TEN has been reported in Han Chinese and Thai population.[7] In Thai population, the prevalence of HLAB*1502 was found to be in the range from 8.1 to 14%.[8] If the patients were not sufficient medical controlled or were poorly tolerated to medication, surgical therapy should be considered. Most well-known surgical therapies for TN are microvascular decompression (MVD), gasserian ganglion percutaneous techniques, and gamma knife. MVD was recommended as the first-line surgery in patients with classical TN.[3, 4] In long-term outcome of MVD studied in 1,185 patients, the annual rate of recurrence was less than 2% by 5 years and less than 1% by 10 years. However, major complications included two deaths shortly after the operation (0.2 %), one brain-stem infarction (0.1 %), and sixteen patients (1 %) had ipsilateral hearing loss.[9] Some patients might not accept the risk of complications or might not be compatible with the surgery.

Botulinum toxin, especially type A has been reported to be useful in various types of neuropathic pain. The mechanism involves inhibiting the release of inflammatory mediators and peripheral neurotransmitters from sensory nerves.[10] There were certain clinical trials suggested that BTX-A might be an effective and safe treatment for patient with TN.[11-14] To clarify that BTX-A is effective in controlling pain in TN, we conducted a pilot clinical trial in patients with refractory TN using low

dose BTX-A and adapted several techniques to reduce the adverse effects. In our study, we use Neu-botulinumtoxinA (Neuronox®) which is BTX-A produced by the Hall A strain of Clostridium botulinum and purified to produce a homogeneous 900-kD toxin complex. It has been approved for various therapeutic and cosmetic indications in some Asian and Latin American countries and has several clinical trials in neurological indications including cervical dystonia, hemifacial spasm, blepharospasm, and post-stroke upper limb spasticity.[15-17]

Materials and methods

Study design

This study is an open-label pilot clinical trial and was approved by the ethics committee of Prasat neurological institute. The detail of clinical study including objective, method and possible adverse reactions were explained to each patient before the study. Informed consent was obtained from all participants prior to study. Patients were free to discontinue the trial at any time during the study period.

This study aims to evaluate the efficacy and safety of BTX-A in patients with refractory idiopathic or classical TN.

Eligibility and enrollment criteria

Eligible participants were recruited from outpatients of neurological department of Prasat neurological institute from June, 2018 to November, 2018. All were diagnosed with classical or idiopathic Trigeminal neuralgia according to the ICHD-III and underwent brain MRI to rule out secondary etiologies. In all patients, pain was intractable. We defined intractable pain as a failure to experience at least a 50% reduction on pain intensity qualified by Visual Analogue Scale (VAS) or paroxysms frequency during the last 3 months, despite the use of proper drugs and dosages. These included patients who cannot tolerate to side effects of drugs or who have allergy to drugs. At baseline, all patients already received medication (e.g. carbamazepine, gabapentin, or baclofen) to control pain. These medications remained unchanged during the period of the study.

Exclusionary criteria

Exclusion criteria were included: trigeminal neuralgia with ophthalmic branch (V1), secondary TN (abnormal structural lesion demonstrated by MRI), pregnancy or breastfeeding patients, underlying disease that increased risk side effect from BTX-A (for example: myasthenia gravis), subjects with known hypersensitivity to BTX-A, and skin infection at injection sites.

Intervention

All of the interventions were administered in the treatment room at the Department of Neurology, Prasat Neurological Institute and was performed by well-trained neurologists who had more than 10-year experiences in BTX-A injection. Botulinum toxin type A was obtained from Medytox company by the trade-name Neuronox®. For intervention, All of patients were received 25 units of BTX-A applied at 10 points (0.05 ml, 2.5 units per point) into the painful trigger points in branches of trigeminal nerve using intradermal and subcutaneous techniques (Figure1 a, b). During the procedure, the danger areas including depressor anguli oris muscle (DAO), risorius, and depressor labii inferioris (DLI) were avoided to prevent unwanted facial asymmetry (Figure1c).

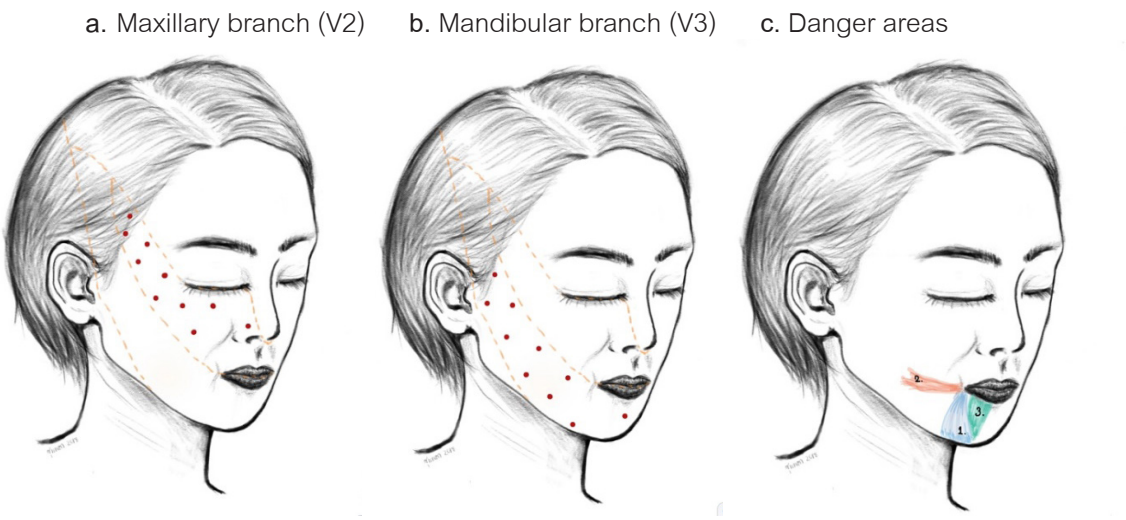

Figure 1 Painful trigger points in branches of trigeminal nerve.
1, Depressor anguli oris (DAO); 2, Risorius; 3, Depressor labii inferioris (DLI)

Efficacy and safety measures

The primary outcomes were pain severity assessed by visual analogue scale (VAS) and attack frequency per day (F) compared before and after receiving BTX-A. All patients have to do the diary by recording the intensity and frequency of the pain that they experienced before going to bed. The duration of diary recording was one week before and eight weeks after receiving BTX-A. The secondary outcomes were quality of life assessed by two questionnaires: Penn Facial Pain Scale-Revised (Penn-FPS-R)[18] and QoL scale. The scores from these questionnaires were compared from baseline to 4th and 8th week after BTX-A injection.

In subgroup analysis, the definition of responder was the patient with an improvement in either VAS or frequency ≥ 50% from baseline.

Examination of the patients were performed before treatment and after the first week, the fourth week and the eighth week of treatment. The result of the examinations and the side effects were recorded at these stages.

Statistical analysis

Simple descriptive analysis in the form of median, means, and standard deviations were calculated for numerical data. Qualitative data were described using percent distribution.

For primary and secondary outcomes, comparison from baseline to endpoints were conducted using Wilcoxon Signed Ranks Test.

In subgroup analysis, factors in responder and non-responder groups were compared using Mann-Whitney test and Fisher's exact test.

The SPSS software (Version17.0) was used for statistical analysis. The level of significance was set at 0.05.

Results

Participant characteristics

A total of 12 Thai patients were included, age ranged from 47 to 80 years (median 57.5, IQR 20.5). They were 7 females (58.3%) and 5 males (41.7%). The duration of the disease was ranged from 2 to 15 years (median 5.5, IQR 4.25). Pain affected one distribution in 8 patients, while two distributions were affected in 4 patients (Table 1).

Table 1 Baseline demographics and characteristics

Patients	Sex	Age (years)	Duration (years)	Affected branch	MRI	Concomitant drug	Remarks
1	F	48	8	Left V2	Vascular loop	Carbamazepine Baclofen Phenytoin Amitriptyline	
2	F	47	2	Left V3	No vascular loop	Baclofen Gabapentin Amitriptyline	- *HLAB*1502:positive*
3	F	48	3	Right V2	Vascular loop	Lamotrigine Baclofen Gabapentin Amitriptyline	- *HLAB*1502: positive*
4	F	53	2	Left V2	No vascular loop	Carbamazepine Baclofen Gabapentin Nortriptyline	
5	M	70	12	Left V3	No vascular loop	Carbamazepine Gabapentin	
6	M	62	15	Right V2 &3	No vascular loop	Carbamazepine Baclofen	
7	F	80	4	Right V2 & 3	Vascular loop	Carbamazepine Pregabalin	
8	F	54	7	Right V2 & 3	No vascular loop	Lamotrigine Topamax Pregabalin Tramadol	- *HLAB*1502: negative* - *Drug allergy: CBZ*
9	M	68	3	Left V2	Vascular loop	Gabapentin Baclofen	- *HLAB*1502: negative* - *Drug allergy: CBZ (DRESS)*
10	M	61	7	Right V2&3	No vascular loop	Carbamazepine Pregabalin Amitriptyline	
11	F	47	6	Left V2	No vascular loop	Carbamazepine	
12	M	79	5	Right V3	Vascular loop	Carbamazepine Gabapentin	

Injection paradigm

Overall, the enrolled 12 patients completed the 8-week period after the intervention.

Efficacy results

Primary outcomes

The median baseline pain score was 7 as measured by the VAS scores (median=7, IQR 1.775). Pain intensity began to reduce as early as first week. The pain reduction reached the bottom at fourth week after injection. The reduction was maintained over the follow-up visits (Figure 2). Pain reduction at the 8-week endpoint was 4.5 which significantly decreased from baseline (P = 0.05). The median attack frequency baseline was 7.69 per day and initiated to reduce at first week after BTX-A

injection. This reduction was continued over the follow-up visits (Figure 3). The frequency at the end of the study was 2.46 per day which significantly reduced from baseline (P = 0.002).

In relation to primary outcomes, almost patients showed the reduction in VAS after the intervention or improved regarding frequency of attacks per day (Table 2). Responders were defined as patients with ≥ 50% improvement in VAS or F from baseline to 8-week endpoint. Based on this criteria, there were 8 patients responded to the treatment. The response rate was 66.67%.

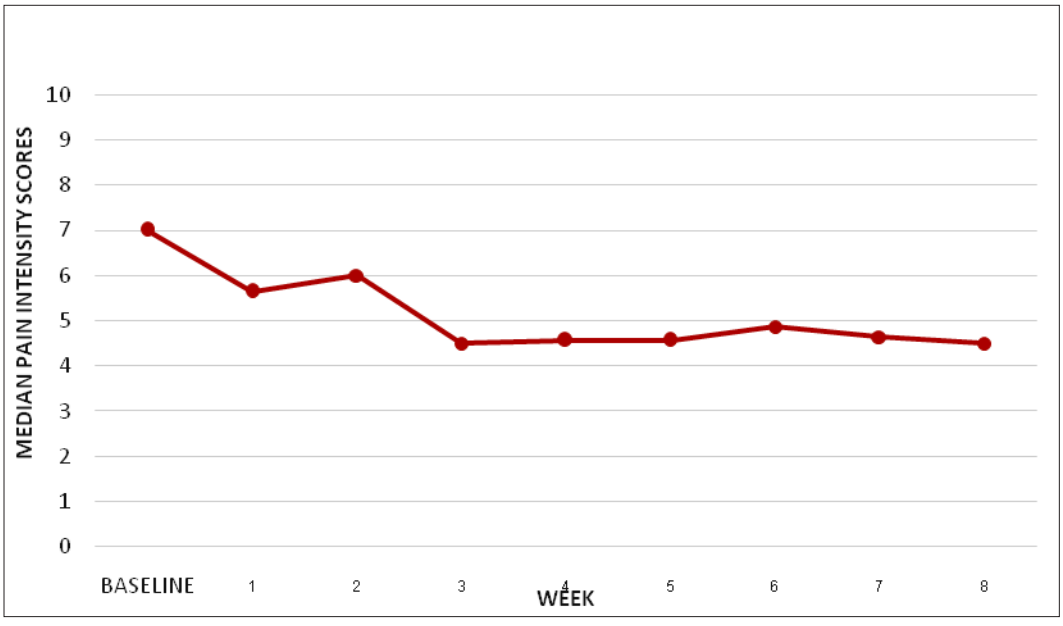

Figure 2 Weekly median pain intensity scores as measured by VAS

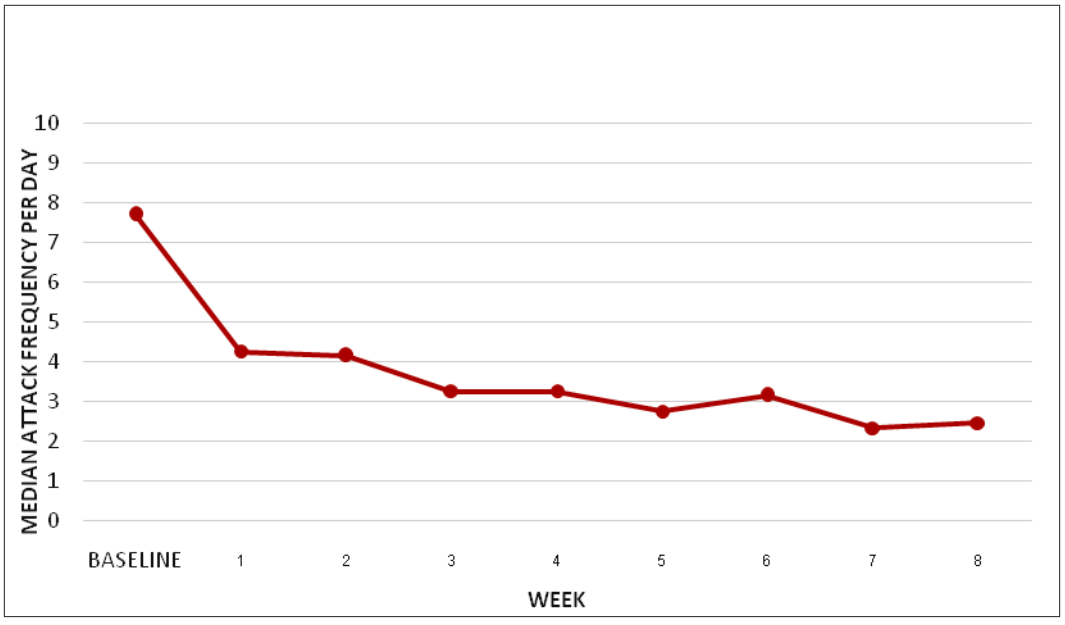

Figure 3 Weekly median attack frequency per day

Table 2 Median pain severity and frequency over treatment course

	Severity of pain (VAS)			Frequency of attacks (per d)		
Patient	Baseline	W_4	W_8	Baseline	W_4	W_8
1	6	6	4.3	8.8	6.1	3.6
2	8.6	7.4	6.7	19.7	17	15.9
3	7.7	4.1	5.7	20	2.5	2.5
4	10	10	10	15	10	10
5	6.5	1.1	0	6.6	0.9	0
6	7	8	6.6	6	3.6	4
7	9.1	1.6	0.3	10	3.5	0.6
8	4	2	1.4	4.9	3	1.5
9	6.7	5.1	4.7	3	2.7	1
10	8	5	1.4	10.7	6.7	2.4
11	6	4.1	6.4	5.6	3	3
12	7	4	4	4	2	2

VAS, Visual analog scale; W_4, 4 weeks after injection; $W_{8,}$ 8 weeks after injection

Secondary outcomes

There was a statistically significant improvement in patient's quality of life as shown in QoL functioning scale and all 12 modalities of Penn FPS-R (Table 3).

Table 3 Secondary outcome

	Baseline	After 8 weeks	p-Value
QoL scale	6.5	8	0.003
Penn-FPS-R			
1) Daily activities	7	4.5	0.006
2) Mood	8	3.5	0.003
3) Relationships	7	3.5	0.003
4) Eating a meal	8.5	5	0.003
5) Biting or Chewing	9	5	0.002
6) Touching face	8	3	0.005
7) Facial self-care	9	3.5	0.002
8) Brushing or flossing	8.5	3.5	0.002
9) Smiling or laughing	8.5	3	0.003
10) Talking	9	4	0.003
11) Opening mouth wide	9	4	0.005
12) Temperature change	6.5	2.5	0.002

Subgroup analysis

Response of BTX-A injection was studied in subgroup analysis according to patients'age, sex, duration of disease, baseline VAS, baseline frequency, affected branch, MRI finding and concomitant use of CBZ. According to all parameters assessed, there were no statistically significant differences between responder and non-responder group. However, there were some tendencies demonstrated in age and MRI finding. In responder group, patients tended to be older and were diagnosed with classical TN as vascular loop presented on MRI.

Table 4 Subgroup analysis

	Responders (n=8)	Non-responders (n=4)	P-value
Age	64.5	50	0.088
Sex (F:M)	4:4	3:1	0.576
Duration (years)	6	4	0.495
Baseline VAS	6.85	7.8	0.394
Baseline Frequency	7.7	10.5	0.497
Affected branch			1.0
V2	3	2	
V3	2	1	
V2 and V3	3	1	
MRI: vascular loop	5	0	0.081
Concomitant drugs			
CBZ	5	3	1.0
Gabapentinoid	7	2	0.236
Baclofen	3	3	0.545
Lamotrigine	2	0	0.515
Tricyclic antidepressant	3	2	1.0
Phenytoin	1	0	1.0
Topamax	1	0	1.0
Tramadol	1	0	1.0

Safety and tolerability

BTX-A injection was tolerated. No systemic reaction was noted and there were no serious injection-related adverse events. The reported side effect was facial asymmetry during voluntary movement in only one patient which automatically recovered in 4 weeks without any further treatment.

Discussion

TN is an extremely painful condition. Mostly, the pain was well controlled by carbamazepine as the first-line treatment. However, there are some patients who initially response well but later start to be refractory after decades.[6] The patients with intractable TN should be offered the surgical therapies, but some may not be compatible with the surgery. Before further invasive procedures, there were several options to treat refractory TN such as intranasal lidocaine, blocking the trigger points with ropivacaine, etc. Among those options, there are increasingly strong evidences that BTX-A injection are efficacious.[19] In the action on neuropathic pain, BTX-A is supposed to block TRPV1 (transient receptor potential cation channel, subfamily V, member 1) receptors of unmyelinated C fibers and limit the release of substance P, calcitonin-gene-related peptide (CGRP), and glutamate from presynaptic terminals of primary sensory neurons.[20] The evidences of BTX-A in TN were first described in several case reports.[21, 22] Since then, there were many pilot-clinical trials[23-25]and RCTs.[11-14]

BTX-A injection in these clinical trials differed in terms of dosage, dilution, injection techniques, units per site, and sources. (dosages ranging from 20 to 100 units per patient and injection site ranging from 1 to 20)[26] Regarding safety, no significant adverse effects were noted.[27] Between 10% to 40% of patients in these previous clinical trials developed mild facial asymmetry, which was transitionary in nature[11,12,14] and may be correlated to sites of

injection, dilution and dosage. In short-term, low dose(25U) and high dose(75U) yield similar efficacy as demonstrated by Wu et al[13]. In another RCT, Shehata et al.[11] suggested that there was no significant correlation between the total injected dosage of BTX-A and efficacy.

In our study, the source of BTX-A was provided by Medytox company by the trade-name Neuronox®. In order to the minimize the incidence of facial asymmetry, we used the low dose of BTX-A (25U/ saline 0.5 mL), and avoided injection in the danger area that is the location of three crucial muscles used for lower facial movement. These muscles are depressor anguli oris (DAO), risorius, and depressor labii inferioris (DLI).

In our study, pain intensity and attack frequency began to reduce as early as first week after BTX-A injection and maintained over the follow-up visits. The patient's quality of life was improved as measured by QoL scale and Penn FPS-R which consisted of 12-item health related quality of life (HRQoL) outcomes that is actual specific to trigeminal neuralgia in order to assess and monitor the impact of treatments or interventions.[18] In our pilot trial, the responder rate was 66.67% (n=8/12). The definition of responder was patient with ≥ 50% improvement in either VAS or frequency from baseline to endpoint. Some previous studies also reported their responder rate as secondary outcome. In 2011, Wang et al.[12] conducted RCT and reported 68.18% (n=15/22) responded to the treatment in the BTX-A group. In 2014, Wu et al[13] reported the response rate 70.4% in 25U BTX-A group (n=19/27) and 86.2% in 75U BTX-A group (n=25/29). However, the definitions of the responders differed among these studied.

We also did the subgroup analysis to evaluate the efficacy of BTX-A injection in various patient's characteristic. There were some correlations demonstrated in the age and MRI findings, but they were not statistically significant. In responders, patients tended to be older and vascular loop were found in 5 among 8 patients. However, the implications should be cautiously interpreted due to small sample size of the study.

The reported side effect in our study was facial asymmetry, which was seen in only one male patient that was well tolerated and recovered in four weeks without any further treatment. Due to our injection technique, the incidence of facial asymmetry in our trial was lower than previous studies (8.3%, 10-40%) respectively.

Overall, the results of the current study support the possible role of BTX-A in treatment of refractory TN as same as previous studies. Additionally, our clinical trial also illustrated in details of the improvement in patient's quality of life as measured by both QoL scale and Penn FPS-R.

There are several limitations of our study. First, the sample size was relatively small. Second, the study was designed as single arm clinical trial which lacked placebo-controlled comparison group. Further well-designed RCTs including an appropriate number of patients will be required to validate our findings.

Conclusion

In summary, the results of this 8-week pilot clinical trial. BTX-A injection would offer some distinct advantages over existing therapies with respect to efficacy and safety.

Disclosure

The authors declared no conflicts of interest in this study.

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