

The effects of intradermal botulinum toxin type a injections on pain symptoms of patients with diabetic neuropathy

Majid Ghasemi, Maryam Ansari, Keivan Basiri, Vahid Shaigannejad

Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran

Background: Considering the dramatic increasing rate of diabetes and consequently its related complications, most importantly diabetic peripheral neuropathy (DPN), challenges regarding proper treatment of DPN and its effect on the quality-of-life and care of diabetic patients, the aim of this current study is to evaluate the effect of intradermal botulinum toxin type A (BTX-A) injections on pain symptoms of patients with diabetic neuropathic pain. **Materials and Methods:** In this randomized double-blind placebo-controlled clinical trial study, diabetic patients aged <70 years with neuropathic pain in both feet were enrolled. Diabetic neuropathy (DN) in selected patients was diagnosed using DN4 questionnaire and nerve conduction velocity examinations. They randomized in two intervention (BTX-A injection/100 unit, $N = 20$) and placebo groups (normal saline injection, $N = 20$). The outcome of injection on diabetic neuropathic pain was assessed using neuropathy pain scale (NPS) and visual analog scale (VAS) score and compared in two studied groups. **Results:** There was no significant difference in DN4, NPS and VAS scales of studied population after intervention in the placebo group. Intradermal injection of BTX-A reduced NPS scores for all items except cold sensation ($P = 0.05$). It reduced DN4 scores for electric shocks, burning, pins and needles and brushing ($P < 0.05$). According to VAS scale 30% and 0% of patients in intervention and placebo groups have no pain after intervention ($P = 0.01$). **Conclusion:** Intradermal injection of BTX-A is a well-tolerated agent that has a significant effect on DPN pain.

Key words: Botulinum toxin type A, diabetic peripheral neuropathy, pain

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INTRODUCTION

Diabetes is one of the most common causes of neuropathy. Diabetic peripheral neuropathy (DPN) is the leading cause of morbidity and mortality in this group of patients.^[1] It is characterized with symptoms such as pain, paraesthesia and sensory loss predominantly in lower extremities due to the peripheral somatosensory system involvement.^[2,3] In addition, DPN is associated with an impaired quality-of-life and psychological problems in diabetic patients.^[4]

Prevalence of DPN has reported to be 10-26% depends upon using criteria for diagnosing DPN.^[5]

Though many analgesic agents including anti-depressants, carbamazepine, gabapentin, opioids and more recently, duloxetine and pregabalin have been introduced for management of DPN, but it seems that already mentioned pharmacologic treatments are not appropriate enough due to lack of long-lasting pain relief, poor tolerability and side-effects.^[6-8] So, mentioned factors in addition

to increased health-related costs of DPN made it as a challenging issue which need further investigations.

In order to avoid the limitations of mentioned analgesic agents, recently the use of topical agents such as lidocaine patches, high-dose capsaicin and botulinum toxin type A (BTX-A) have been developed. Though the effectiveness of these agents for pain relief of DPN was not confirmed in all studies, but the superiority of them, their minor systemic side-effects, made their use more favorable in this regard.^[9-11]

BTX-A is a potent neurotoxin, which commonly used for the treatment of dystonia, muscle hyperactivity and glandular hyperactivity.^[12,13] Some evidences suggests that regardless of its myorelaxant action, BTX-A might have analgesic properties for DPN.^[14,15]

Although the mechanisms of its analgesics effect was not determined clearly, but evidences from *in vitro* and *in vivo* experiments demonstrated the analgesics effect of BTX-A injection on neuropathic pain of diabetic patients.^[14-18]

Address for correspondence: Dr. Maryam Ansari, Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: maryamansari1386@gmail.com

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Considering the dramatic increasing rate of diabetes and consequently its related complications most importantly DPN, challenges regarding proper treatment of DPN and its effect on the quality-of-life and care of diabetic patients, the aim of this current study was to evaluate the effect of intradermal BTX-A injections on pain symptoms of patients with diabetic neuropathic pain.

MATERIALS AND METHODS

In this randomized double-blind placebo-controlled clinical trial study, 57 type 2 diabetic patients aged <70 years with neuropathic pain in both feet referred to neurology clinics of Al-Zahra and Kashani Hospitals, affiliated to Isfahan University of Medical Sciences, from September 2011 to September 2012, were enrolled.

The protocol of the study was approved by Regional Bioethics Committee of Isfahan University of Medical Sciences (Research Project Number: 390565).

The patients were selected by simple randomized sampling method. Written informed consent was obtained from all selected patients.

There were also prerequisites that the medication for neuropathic pain had not been changed within the previous 1 month period and during the course of the trial.

Diabetic neuropathy (DN) (symmetrical distal sensory and motor polyneuropathy) in selected patients was diagnosed using DN4 questionnaire and nerve conduction velocity (NCV) examinations.

Patients with no appropriate cooperation, hypersensitivity reaction to BTX-A and those who currently use other analgesics for their neuropathic pain were excluded. In addition those with an infection at the injection site, any lumbar-sacral radiculopathy based upon clinical presentation, neurologic examination and electrodiagnostic (EDX) study, motor deficit, alcoholism and renal function impairment, distal muscle weakness and atrophy, history of myasthenia gravis, concomitant usage of aminoglycosides and breastfeeding mothers were excluded from the study.

Other causes of DN was determined in each case separately according to his/her medical file and presented documents. In conflicting case, further diagnostic test was done.

Selected patients were randomized in two intervention (BTX-A injection) and placebo groups (normal saline injection).

The injections will be distributed across the dorsum of the foot, in a grid distribution pattern covering a total of 12 (3 × 4) sites. The distribution of these sites will be such that the distance between them was approximately equal. To keep the study blind, the preparation of saline and BTX-A was performed by an independent study physician, who did not participate in the interview of participants.

One hundred units of BTX-A (Dysport-Ipsen, UK) in 0.9% saline were then administered intra-dermally into one foot, with each injection comprising approximately 8-10 U BTX-A, using an insulin syringe.

Nearly 0.9% saline injections were performed in an identical manner.

The outcome of injection on diabetic neuropathic pain was assessed using neuropathy pain scale (NPS) and visual analog scale (VAS) scores by Neurologist.

The outcome of injection was evaluated 3 weeks after injection. The effect of injection was first compared in each group before and after injection and then the outcome of injection was compared between groups.

DN4 questionnaire

DN4 is a clinician-administered questionnaire. It consists of both sensory descriptors by interview and signs based on bedside sensory examination. It has a high level of sensitivity and specificity in discriminating neuropathic from nociceptive and somatic pain and can help in the correct detection of neuropathic pain.^[19]

The patients should have four or more items positive among the 10 items of the DN4 questionnaire to enter the study.

NCV examinations

The NCV examination should show a reduction of amplitude in peroneal, tibial or sural nerve down to the normal lower limit value. EDX findings suggestive of chronic axonal distal sensorimotor poly neuropathy in lower extremities.

No alterations were made to the prescribed medications for neuropathic pain during the study period.

NPS

The NPS contains an introduction describing how people may experience pain sensations differently and how unpleasantness differs from intensity.

The scale presents 10 domains of pain, including two items that assess global pain intensity and pain unpleasantness and eight items that assess the specific qualities or locations

of neuropathic pain: Sharp, hot, dull, cold, sensitive, itchy, deep and surface.

Subjects were asked to rate each quality of pain on a scale of 0-10, where 0 = no pain or not _____ (item) and 10 = the most _____ (item) sensation imaginable.

The validity of NPS was proved in a trial by Jensen *et al.*^[20]

VAS score

For VAS measurement, we asked the patients to point out the current pain severity during the last day on a rule with 0.0-10.0 scales (0.0 - no pain, 10.0 - unbearable pain).

Statistical analysis

Obtained data is analyzed using SPSS (Release 18.0, SPSS Inc., Chicago, IL, USA).

Baseline characteristics of studied population were compared using Student *t*-test and Chi-square test. DN4 score in the placebo and intervention groups before and after the intervention was compared using McNemar test. Mean ± standard deviation (SD) of NPS score in the placebo and intervention groups before and after the intervention was compared using independent and paired *t*-tests. *P* < 0.05 was considered to be statistically significant.

RESULTS

In this study, 40 (22 men and 18 women) patients fulfilling the inclusion criteria and randomized in two placebo and control groups (20 in each groups

[Figure 1]. After randomly patients selection in two groups, *t*-test and Chi-square tests indicated that there were similar according to sex and age and insulin use [Table 1]. If they were not similar we would use ANCOVA and Chi-square for ANCOVA tests.

Baseline characteristics of the studied population in the placebo and intervention groups are presented in Table 1.

DN4 score in the placebo and intervention groups before and after intervention (3 weeks later) is presented in Table 2.

Mean ± SD of NPS score in the placebo and intervention groups before and after intervention (3 weeks later) is presented in Table 3.

According to VAS scale 6/20 (30%) and 0% of patients in intervention and placebo groups have no pain after intervention (*P* = 0.01). 7/20 (35%) of patients in the intervention group showed bilateral pain reduction.

There was not any report regarding the side-effects of BTX-A injection in the studied population.

Table 1: Baseline characteristics of studied population in placebo and intervention groups

Variables	Placebo group, n = 20	Intervention group, n = 20	P value
Age (years)	59.3±9.6	62.7±9.9	0.26
Sex (male/female)	9/11	13/7	0.20
Insulin therapy (%)	12 (60)	10 (50)	0.33

The results are presented as mean ± SD or *n* (%) where appropriate; SD = Standard deviation

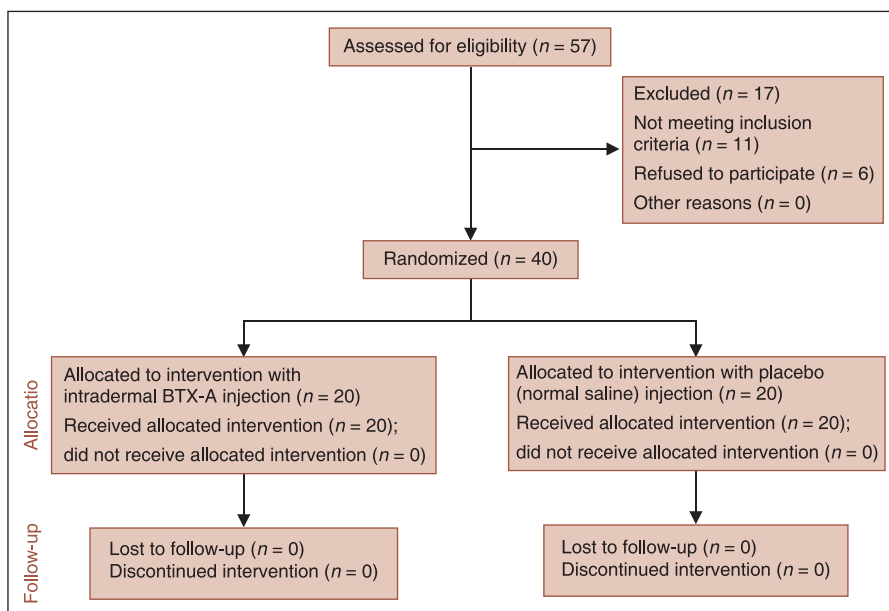


Figure 1: Consort flow diagram of the clinical trial

Table 2: DN4 score in placebo and intervention groups before and after intervention (3 weeks later)

Items	Placebo group		P value	Intervention group		P value
	Before intervention %	After intervention %		Before intervention %	After intervention %	
Painful cold	60	55	0.95	35	25	0.5
Electric shocks	50	40	0.5	50	15	0.01*
Burning	80	80	1	100	30	<0.01*
Tingling	100	100	1	100	90	0.5
Pins and needles	100	100	1	100	75	0.03*
Numbness	75	75	1	90	90	1
Hypoesthesia to touch	65	65	1	50	40	0.5
Hypoesthesia to pin prick	65	65	1	50	40	0.5
Brushing	55	55	1	55	5	<0.001*

*Using McNemar test; DN4 = Diabetic neuropathy 4

Table 3: Mean ± SD of NPS score in placebo and intervention groups before and after intervention (3 weeks later)

Items	Groups	Before intervention	After intervention	P value within groups
Pain intensity	Placebo	7.1±2.2	7.0±2.0	0.8
	Intervention	6.9±2.1	5.1±2.3	<0.001
	P value between groups	0.76	0.009	-
Sharp sensation	Placebo	5.4±2.6	4.9±2.6	0.1
	Intervention	5.4±2.4	4.2±2.7	<0.001
	P value between groups	0.95	0.41	-
Hot sensation	Placebo	6.3±2.7	6.6±2.2	0.3
	Intervention	6.6±2.9	4.3±2.5	<0.001
	P value between groups	0.69	0.005	-
Dull sensation	Placebo	4.5±2.2	4.5±2.2	1
	Intervention	4.8±2.1	3.2±1.6	<0.001
	P value between groups	0.66	0.03	-
Cold sensation	Placebo	4.1±4.0	3.8±3.8	0.33
	Intervention	3.7±3.6	3.1±2.9	0.05
	P value between groups	0.74	0.55	-
Sensitive sensation	Placebo	5.5±2.3	5.5±2.3	1
	Intervention	5.5±3.7	4.0±2.8	<0.001
	P value between groups	1	0.03	-
Unpleasant sensation	Placebo	7.4±1.5	7.2±1.6	0.16
	Intervention	7.4±1.2	5.1±1.8	<0.001
	P value between groups	1	<0.001	-
Deep pain	Placebo	7.5±1.2	7.4±1.3	0.16
	Intervention	6.8±2.4	5.3±1.6	<0.001
	P value between groups	0.28	<0.001	-
Surface pain	Placebo	5.8±2.5	5.8±2.5	1
	Intervention	5.6±2.5	4.2±2.6	<0.001
	P value between groups	0.75	0.04	-

NPS = Neuropathy pain scale; SD = Standard deviation

DISCUSSION

In this study, the effect of intradermal BTX-A on neuropathic pain of diabetic patients was studied, the findings indicated that almost all studied NPS items were improved after BTX-A administration except for cold sensation, whereas there was not significant effect in this regard in the placebo group.

The analgesic effects of BTX-A in DPN in both animal and human population have been more recently studied.^[14-18]

The advantages of BTX-A administration for mentioned purpose are its efficacy, extended duration of its analgesic effects, well tolerability and less side-effects.^[21] Although there were still limited number of trials regarding the usefulness of BTX-A administration for treatment of DPN but almost all existing studies supported its effectiveness in this regard.

The beneficial effect of BTX-A is believed to result from the blockade of presynaptic nerve terminals releasing acetylcholine, but its exact analgesics effect was not

determined yet.^[22-24] Ranoux *et al.* suggested that the analgesics effect of BTX-A is may be due to its local peripheral effect on nociceptive fibers.^[14]

Some experimental studies have indicated the effects of BTX-A on DN model in rats. Bach-Rojecky *et al.* in Croatia have investigated antinociceptive activity of BTX-A in a model of DPN pain in rats. They demonstrated that unilateral BTX-A injection result in bilateral pain reduction with long-lasting effect up to 4 weeks.^[25]

Ranoux *et al.* in France studied the analgesics effects of one-time intradermal administration of BTX-A on DPN pain in 29 diabetic patients. The outcome was reported at baseline, 4, 12 and 24 weeks after injection. They indicated that BTX-A have a significant effect on pain intensity of DPN from 2 to 14 weeks after injection. For the 1st time, they concluded that BTX-A independent of its action on muscle tone have an analgesic effect on DPN pain. Hence, chronic DPN related pain considered as a novel indication for intradermal BTX-A injection.^[14]

In another recent study, Ranoux in France reported that one session of multiple intradermal BTX-A injection have long-lasting analgesic effects in patients with DPN. The results were compatible with a reduction of peripheral sensitization.^[21]

Yuan *et al.* in Taiwan, in a double-blind crossover trial have investigated the effect of intradermal BTX-A for DPN pain in 20 patients. They showed that using VAS, BTX-A significantly reduced DPN pain during a 12-week period. Nearly 44.4% of their studied patients reported VAS reduction regarding DPN pain within 3 months after injection.^[15]

The findings of the current study were in line with mentioned study but we did not study the long-term effect of BTX-A in this regard. According to VAS scale 30% of patients in the intervention group have no pain after intervention. The results of our study showed that all studied pain domains, studied by NPS score, significantly decreased. Regarding cold sensation *P* value was 0.05.

DN4 scores among studied population in interventional (BTX-A) group showed a significant reduction in electric shocks, burning, pins, needles and brushing. They did not show a significant difference in reminder items.

It seems that it may be due to small sample size but for more conclusive result it should be evaluated in future studies.

BTX-A usually administrates intramuscularly for focal spasticity or dystonia but in this study we evaluated intradermal effect of BTX-A for DPN pain. Considering the extent of the painful area and safety of the procedure, it seems that this form of injection is more favorable for DPN pain treatment than intramuscular form.

The advantage of our study was that we used NPS score for outcome measurement. However, because neuropathic pain is associated with a variety of pain sensations, the effects of any treatment on different sensations could go undetected if specific pain qualities are not assessed. So, we used NPS score which evaluate the variety of pain sensation.

The limitation of this study was that the outcome of BTX-A injection in DPN pain was evaluated for a short time, i.e., 3 weeks after injection and the long-term effect of BTX-A was not studied due to the problems regarding patients regular follow-up. This limitation should be considered in our future studies; however the results would be important in clinical practice for proper management of DPN pain.

CONCLUSION

Based on the limitations of this study, it can be concluded that intradermal injection of BTX-A has a significant effect on DPN pain and it is a well-tolerated agent for the purpose. Although obtained results suggest that BTX-A could be an appropriate therapeutic agent in this field, but for more conclusive result and better DPN pain management protocol further large scale studies with long-term follow-up period is warranted.

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