Botulinum Toxin Type A in Severe Diabetic Neuropathy

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Abstract:

Background: Managing patients with severe diabetic neuropathy is a great challenge, many lines of treatment are available but there are many patients that cannot tolerate large doses of these medications or not responding or contraindicated to use these lines. Recent experimental evidence suggests that botulinum toxin type A (BTX-A) may have role in management of neuropathic pain. **Methods**:42 patients with diabetes(22 patients injected Botox and 20 patients placebo) were enrolled in this study. Patients were assessed using VAS and PSQI scale at 0,1,4,12 weeks. **Results**: significant reduction in VAS 1,4- and 12-weeks post injection in patients injected with Botox in comparison to patients injected with placebo p (.047,.001 and .000) respectively. No significant improvement in PSQI in patient injected with Botox as compared to patients injected with placebo. **Conclusion**: Botulinum Toxin (A) is effective in sever diabetic neuropathy and may be an alternative way in management of severe diabetic neuropathy.

Key words: Botulinum toxin type (A), diabetic neuropathy, neuropathic pain.

Introduction

Diabetic peripheral neuropathy (DPN) is a common complication of diabetes affecting 66% of patients with insulin-dependent diabetes mellitus and 59% of patients with non-insulin-dependent diabetes mellitus (1) . Painful diabetic neuropathy (PDN) affects 16% of patients with diabetes, and it is frequently unreported (12.5%) and more frequently untreated (39%) (2). Neuropathic pain has a substantial impact on quality of life, especially by causing considerable sleep disruption, daily activities, and enjoyment of life. Chronic neuropathic pain is present in 13–26% of

diabetic patients. (3-6) Chronic DPN with persistent or episodic pain that typically may worsen at night, and improve during walking, is localized predominantly in the feet.

The pain is often described as a deep-seated ache, but there may be superimposed lancination, or it may be of burning thermal quality (7) More than 25% of patients with type 2 diabetes have neuropathic pain syndromes. The pain, usually attacking the distal extremities, results in disturbed sleep and diminished quality of life (4).

Although many symptomatic therapies are available for neuropathic pain, including antidepressants, anticonvulsants, and opioids, as well as some novel strategies, many of these remain unsatisfactory. A small number of patients do not tolerate the adverse events (8). Botulinum Neurotoxins (BTX-A) are used in treatment of spasticity and glandular hyperactivity but also found to suppress both nociceptor sensitization and neuropathic pain such as trigeminal neuralgia and carpal tunnel syndrome (8, 9).

This effect is due to the inhibition of neurotransmitter release as serotonin, dopamine, noradrenaline, glutamate, gamma aminobutyric acid (GABA), enkephalin, glycine, substance P, ATP, calcitonin gene-related peptide (CGRP), somatostatin, and neuronal nitric oxide synthase. In this study, we evaluated the effects of intradermal, rather than intramuscular, **BTX- A** injections on pain symptoms in patients with diabetic neuropathic pain.

Patients and Methods

This case control study was done January 2012 - March 2013, 42 patients with diabetes (22 patients injected **BTX-A** and 20 patients placebo) in Mansoura University hospitals, and outpatient clinics of Neurology.

Prior to the initiation of the study, all procedures was reviewed by ethical and research committee, Mansoura University. Written informed consents were obtained from all participants, they were informed about the nature and objectives of the study.

These patients were required to have a history of diabetes mellitus and neuropathic pain in both feet with trial of traditional treatment for enough period with maximum tolerable dose or contraindication to these treatments. Diabetic neuropathy was diagnosed by history and nerve conduction study examinations.

Exclusion criteria:

The exclusion criteria included common causes of pain in both lower limbs peripheral arterial occlusion disease, infection and any lumbar-sacral radiculopathy through history, local examination for signs of inflammation , arterial pulsation and examination of back neurological examination to rule out disc prolapse also patients underwent investigations to exclude other causes (X-Ray lumboscaral and arterial suppler on both Lower limbs). Patients stop medication for pain before and after injection to avoid their bias.

Methods

Patients with severe diabetic neuropathy (VAS ≥7) were injected intradermally with **BTX-A** 50 units in each foot in 12 points 3*4 across dorsum of the foot. The distance between them is approximately equal, and also in some target points mentioned by the patient shortly around ankle or above it (maximum three or four points), for the control group patients injected with saline 0.9% in the same points and with the same manner as patients group.

ASSESSMENT

Visual analogue scale (VAS) and Pittsburgh Sleep Quality Index (PSQI), at 0, 1- week, 4-weeks, 12-weeks, and 12-week intervals. For VAS measurement, the study nurse 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). Changes in VAS score within 12 weeks are the primary endpoint and changes in sleep quality are the secondary endpoints for this study.

Statistical analysis

The collected patients' data were tabulated and analyzed using the SPSS version 16 software (SPSS Inc., Chicago, ILL company). Categorical data were expressed as number and % and analyzed using 'χ^2' and Fisher's exact tests. Continuous variables were presented as mean and SD and analyzed using 'Student's *t*-test'. The accepted level of significance in this work was 0.05 (P<0.05 was considered significant).

Results

22 patients 13 male (59.1%) and 9 female (40.9%) were injected with Botox and 20 patients 10 male (50%) and 10 female (50%) were injected placebo mean age (62.73±5.71) for botox group and (62.95±5.81) for the control group (table 1, 2)

Before injection VAS was (8.73±0.46) for patients group and (8.45±0.60) for control group, after 1 week VAS (7.45± 0.86) for patients group and (7.95±00.69) for control group , after 4 weeks VAS (5.95± 0.95) for patients group and (6.85±0.67) for control group and after 12 weeks VAS (5.14± 1.08) for patients group and (6.40±0.6) for control group (table 3).

During follow up of patients injected with botulinum toxin and placebo there was a significant reduction in VAS 1, 4 and 12 weeks post injection, in patients injected with Botox in comparison to patients injected with placebo ($p<0.05$) (0.047, 0.001 and 0.000) respectively as regard improvement of symptoms of burning, evoked pain to brush (table 4) No significant improvement in PSQI 1,4 and 12 weeks post injection in patient injected with BTX-A as compared to patients injected with placebo ($p<0.05$) (0.62 , 0.64 and 0.6) respectively (table 5)

Table 1: Demographic data of patients and control group

			Patients	Control	Total
Sex	**Female**	**Count**	9	10	19
		% within group	40.9%	50%	45.2%
	Male	**Count**	13	10	23
		% within group	59.1%	50%	54.8%
Total			22	20	

Table 2: Age of patients and control group

		Number	Mean	Std. Deviation
Age	**Patients**	22	62.73	5.71
	Control	20	62.95	5.81

Table 3: Comparison of the effects of BTX-A and placebo on (VAS) at 0, 1, 4, 12 weeks post injection

		Number	Mean	Std. Deviation
VAS 0	**Patients**	22	8.73	0.46
	Control	20	8.45	0.60
VAS 1	**Patients**	22	7.45	0.86
	Control	20	7.95	0.69
VAS 4	**Patients**	22	5.95	0.95
	Control	20	6.85	0.67
VAS 12	**Patients**	22	5.14	1.08
	Control	20	6.40	0.6

Table 4: Comparison of the effects of BTX-A and placebo on (VAS) at 0, 1, 4, 12 weeks post injection

Visual analogue scale	P-value
VAS 0	0.105
VAS 1	0.047
VAS 4	0.001
VAS 12	0.000

Table 5: Comparison of the effects of BTX-A and placebo on (PSQI) at 0, 1, 4, 12 weeks post injection

Pittsburgh Sleep Quality Index	P-value
PSQI 0	0.46
PSQI 1	0.62
PSQI 4	0.64
PSQI 12	0.6

Discussion

The analgesic effects of BTX-A in DPN in both animal and human population have been studied (10, 11, 12). The advantages of BTX-A administration in server diabetic neuropathy over ordinary treatment due to its efficacy, extended duration of its analgesic effects, well tolerability and less side-effects (10). Although there were still limited number of trials regarding the usefulness of BTX-A administration for treatment of DPN but most of existing studies supported its effectiveness in this regard.

An important issue in our study is the application on severe pain associated with diabetic neuropathy which is specifically considered in this study as those patients has long history of medical treatment and most of them are resistant to treatment. 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 (14-16).

Ranoux and co-workers, suggested that the analgesics effect of BTX-A may be due to its local peripheral effect on nociceptive fibers (11). That study conducted in France, was done on 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. They indicated that BTX-A have a significant effect on pain intensity of DPN from 2 to 14 weeks. 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 (10). In another recent study, (14) done using multiple intradermal BTX-A injection, revealed that it has significant improvement in VAS after 3 weeks of injection of patients with DPN. Yuan et al. (12) 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.[12]

Our study showed similar results regarding VAS at 4 weeks and 12 weeks. but with PSQI no significant changes, whereas in the study of Yuan and colleague (12), there was significant improvement in the PSQI which may be due to the persistence of some pain modalities as our study didn't include scale that assess different pain modalities and pain in diabetic neuropathy

may be due to any type which interfere with sleep quality.

Our results regarding the PSOI is not contradictory to the significant improvement in VAS as this may be explained by the psychological feedback of undergoing a new procedure and a new hope to relief pain and the denial to face the fact that, no hope. Also, it seems that this type of treatment improves some modalities of pain and not the other which may be masked during a day and become more prominent at night but when discussing patient he evaluates the overall improvement.

So, we recommend, further application studies on a larger sample of patients with longer period of follow up and the use of more detailed scales for the different modalities of pain for better evaluation.

Conclusion

The use of BTX-A in patients with severe diabetic neuropathic pain may be a new hope for patients resistant to medical treatment or have contraindications to it. Our study revealed significant good results with intradermal injection of BTX-A with minimal side effects and relative less contraindications compared with other drugs but still we need a study on a wide range scale.

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